“Matching Patients with Treatments” (Istvan Petak, MD, PhD) [#107]

Brad Power
July 17, 2024

“The software becomes the new device. We need to implement the real concept of precision oncology and solve the paradigm that we want to provide personalized therapy, and we want to select the targeted therapy based on the molecular profile of the patient. But we want to do this in a way that is evidence-based. The only way to do this is to validate the method we use to choose a personalized therapy.” – Istvan Petak, MD, PhD

“I am most excited about how to shorten the 14 million years we theoretically would need to do all the clinical trials to match the right therapy for every cancer patient. In a review paper in 2019, the authors envisioned that by 2039 we will have clinical trials that do not compare drugs, but AI-based treatment assignment algorithms. This is how we can shift the paradigm in medicine and test the personalized treatment selection methods, instead of individual therapies. We want to make sure that we don't have to wait until 2039. I think the time has come.” – Istvan Petak, MD, PhD

Meeting Summary

Advanced cancer patients want access to therapies that are uniquely selected to them, based on their medical history and genomic and molecular profile. For many cancers, an array of molecularly-targeted agents are approved and available to patients. The complexity of cancer, with its numerous types and genetic mutations, makes the decision on treatments difficult. Each cancer is caused by a unique combination of over six million potential mutations of 700+ cancer genes. The targeted therapies that currently exist are focused on only some of the most frequent cancer genes... and often fail to work due to the complex, unique molecular background of each tumor. Comprehensive molecular testing is key in treatment decisions and interpretation of complex molecular profiles is essential, but can be challenging and subjective.

Istvan Petak, MD, PhD, is uniquely qualified to discuss the challenges of matching a patient's profile with their best treatment plan. Dr. Petak is a biomedical scientist with over 25 years of experience in precision oncology. He is an adjunct professor of molecular pharmacology at the University of Illinois at Chicago (UIC), author of over 150 scientific publications focusing on precision medicine, and founder of the medical technology companies Oncompass Medicine and Genomate Health. He pioneered the molecular pharmacology of programmed cell death in 1998, predictive molecular diagnostics of lung cancer in 2003, and next generation sequencing in molecular profiling of solid tumors in 2008. He led the development of a novel computational method that successfully implemented cognitive computing in precision oncology in 2021. Genomate® helps physicians find the right targeted therapy for every cancer patient based on the individual molecular profile of their tumor. For example, in a recently published study they demonstrated that their solution, an algorithmic computational reasoning model that ranks associated targeted therapies based on the totality of individual tumor genomic data, and using thousands of evidence rather than matching one drug to one biomarker with one evidence, was predictive of relative benefit of the agents. They also collected real-world clinical outcome data

from lung cancer patients who received decision support where digital drug assignment was integrated to aid a molecular tumor board and found higher effectiveness of administered therapies supported by the computational model. These results have been published in peer-reviewed journals and presented at professional meetings.

What are the potential benefits of using your genomic profile and software tools to guide your treatment decisions?

If researchers can identify the molecular mechanism and a target of malignant transformations that create cancer cells, they can often develop an effective therapy. Then you need a diagnostic assay that will identify if you have the target biomarker which will predict if you will respond to that therapy. You get therapies that have the highest probability that they should work for you.

What are the challenges that you may face when you want to implement precision oncology in clinical practice that can be addressed with treatment guidance software?

- There has been slow progress in cancer research due to the large number of mutations that need to be validated if they are really driver mutations.
- Only a fraction of patients have a biomarker that can be derived from a companion diagnostic that is actionable.
- If you have an actionable biomarker, it’s not sure that you will respond to a treatment which targets that biomarker because one of your co-occurring other mutations can alter your response to a therapy.
- If you have multiple tests which identify multiple gene alterations, each can be linked to a specific possible therapy, but there is no way to figure out which one to choose for your specific combination of alterations. If you have multiple options you can choose from, you may not know which one to choose.
- Personalized cancer therapy is often supported by only low level statistical evidence and is associated with low level reproducibility and scalability.
- Molecular tumor boards are one possible solution, but if you send the same molecular diagnostic test results to two boards, concordance on treatment recommendations is only 44-63% according to published investigations.
- Treatment options that come out as being best, but are “off-label” (not approved for this indication), are hard to get reimbursed.
- Your test data inputs may be old and not reflect the current state of your disease.

What do you need as inputs to treatment guidance software?

All test results can be used: DNA sequencing, RNA sequencing, liquid biopsies, immunohistochemistry (staining of tissue slides), FISH (Fluorescence in Situ Hybridization, a test that uses fluorescent molecules to visualize and map the genetic material in a cell's chromosomes)

What’s next in the development of treatment guidance software?

“Matching Patients with Treatments” (Istvan Petak, MD, PhD) [#107]

- More and better algorithmic companion diagnostics identify molecularly-targeted therapies personalized to you, including identification of new indications for therapies (“off label uses”) that will become on-label use of targeted therapies based on your unique molecular profile if FDA approves these new indications.
- Payers will hopefully reimburse algorithmic tests using new codes
- Payers will hopefully automatically approve therapies with a threshold level of certainty and evidence showing a very high correlation to outcomes (even off-label)
- The software can also help accelerate clinical development of novel targeted therapies

How can you learn more?

- See the notes, transcript, and recording from our discussion with Dr. Michael Castro on using AI for treatment selection based on molecular pathways.
- Contact Istvan Petak at istvan.petak@genomate.health.

“Matching Patients with Treatments” (Istvan Petak, MD, PhD) [#107]

Meeting Notes

KEYWORDS

patient, therapy, genetic alterations, test, targeted therapy, molecular, gene, mutations, based, cancer, question, oncologists, model, today, treatment options, target, biomarker, information, alterations, companion diagnostics

SPEAKERS

Istvan Petak (86%), Richard Anders (5%), Roger Royse (4%), Brad Power (3%), Mark Stoner (1%), Adrien Sipos (1%)

CHAT CONTRIBUTORS

Stratis Telloglou, Alina Luchian, Richard Anders, Brad Power, Saed Sayad, Rick Davis, Ari Akerstein

SUMMARY

For personalized cancer treatment, cancer patients, caregivers, and physicians must identify genetic causes and match patients with effective treatments. AI has the potential to revolutionize cancer treatment by providing personalized therapies based on a patient's molecular profile. Regulators and researchers need to review AI-based diagnosis and treatment assignment algorithms, as well as the importance of explainability and transparency in AI-driven diagnostics.

OUTLINE

Introductions and background in using software and technology to match cancer patients with their best treatment options and identifying the genetic causes of cancer and developing targeted therapies.

- Dr. Petak started in pediatric oncology in 1995.
- He was studying why a 5% subset of pediatric leukema patients that harbored the BCR-ABL translocation that were resistant to chemotherapy, that led him to dedicate his life to find the right targeted therapy, that targets the genetic cause, for every cancer patients based on the individual mulecular profile of their tumor.
- Between 1998-2003 he did research on potential molecular targets that regulate cell growth and cell death at St. Jude.
- In 2003, he had a leading role in the first documented successful targeted therapy of a metastatic lung cancer patient based on the presence of a specific mutation published in Journal of Clinical Oncology in 2005. This patint survived more then five years and died of an unrelated cause.
- In 2010, he was the invited author of Nature Reviews Drug Discovery where he predicted that all targeted therapies would need companion diagnostic tests to identify genetic alterations in cancer patients.

- In 2020, a Nature paper reported that whole genome sequencing could identify genetic causes of cancer in 95% of cancer patients, marking the beginning of the post-cancer genomic era.
- In 2021, Dr. Petak and his team published in Nature Partner Journal Precision Oncology the first successful clinical validation of their computational method that enables oncologists to make treatment decisions based on the totality of genetic alterations.

Challenges in personalized cancer treatment.

- There has been slow progress in cancer research due to the limited number of validated driver mutations and the limited actionability of genetic alterations.
- Personalized cancer therapy is hard, due to the low level of evidence and scalability.
- Molecular tumor boards are one possible solution, but they can to scale to address the need of all cancer patients that are treated at community oncologists and there is low concordance between opinions.

Developing a computational reasoning system for identifying targeted therapies for cancer patients based on their molecular profile.

- Researchers analyzed 10,000 cancer cases to develop a mathematical model linking driver genes to targeted therapies.
- Developed an algorithm to predict targeted therapy effectiveness based on individual patient molecular profile.
- The system automates and augments evidence and guideline-based decision making process. Instead of making a decision based on one biomarker and one evidence, the system uses on average 1000 published evidence to generate treatment recommendations based on the totality of alterations.

Using computational models to improve personalized cancer treatment decisions based on molecular profiling and AI.

- Treatment decisions supported with Genomate’s computational clinical decision system had 4x higher response rate and longer progression-free survival based on the clinical trial data of SHIVA01. But more research is ongoing to provide further evidence on the clinical performance of the method to become an FDA-approved diagnostic device in the future.
- There are advancements in personalized cancer treatment using existing diagnostic tests also for immunotherapies.
- AI-based treatment assignment algorithms will be in clinical trials before 2039.
- Oncologists and oncology practices will use AI solutions to personalize cancer treatment.
- Genomate’s AI-powered platform for personalized cancer treatment has used anonymized data to validate their method and increase trust among doctors.
- Doctors will accept the use of algorithms to make better decisions, but they still need to work together with AI developers to create better solutions.

Using machine learning to predict cancer treatment response, with focus on database and algorithm updates, validation, and effectiveness in different tumor types.

- Richard Anders questions the feasibility of analyzing quintillions of datasets with complex drug interactions and toxicity.

“Matching Patients with Treatments” (Istvan Petak, MD, PhD) [#107]

- Dr. Petak in his response tells that researchers update AI model's database and algorithm after testing on validation data sets to improve prediction of therapy response. Real-world evidence and existing clinical trial data can also validate novel software algorithms.

Timing of molecular profiling in cancer treatment.

- Mark Stoner connects with NASA and Institute Curie, discusses microgravity research opportunities.
- Timing of biopsy vs. precision of therapy in cancer treatment.
- Dr. Petak explains that while doing the tests from new biopsy is biologically advantageous he is concerned about delay in starting the next line of therapy. He advises to test as soon as possible and use the information to plan the sequence of therapies.
- Higher clinical utilisation of molecular diagnostics aided by computational tools will increase oncologists' willingness to order tests before starting treatments.

TRANSCRIPT

Brad Power
This is the Cancer Patient Lab.

We're honored to have Dr. Istvan Petak broadcasting from Budapest. I always like it when we're International in our reach.

Some quick housekeeping. This is not medical advice. This is for information purposes only, so that you can take information you get to your medical team.

The Cancer Patient Lab is a patient-led, volunteer-led nonprofit. We would appreciate any donations you might make, which you can do on our website.

Dr. Petak and I had a nice conversation when he was passing through Cambridge on his way to ASCO. I learned of his work in using software and technology to help match patients with their best treatment options, which is of course very central to what we are interested in at the Cancer Patient Lab. I'm sure he'll do a lot more to introduce himself and his topic.

Roger will be moderating.

Istvan Petak 2:02
Thank you very much for having me and inviting me, Brad, and all of you. I am very excited about sharing what you have been working on and trying to achieve.

“Matching Patients with Treatments” (Istvan Petak, MD, PhD) [#107]

Just a few words about myself and the journey. I graduated as an MD 29 years ago in 1995. As a young doctor, I decided to go into pediatric oncology. I was working with pediatric patients, I treated patients with leukemia, In 1995 this was before the human genome era, and it was before the targeted therapy era. It was basically identifying the use of chemotherapy. At that time, we noticed that a fraction of the 5% of acute leukemia patients had a worse prognosis than the average, and we found out that they carried the BCR-ABL translocation, the “Philadelphia chromosome”, that was really the first of the genetic events which link to cancer. We already knew in 1995 that that gene is actually the cause of cancer.

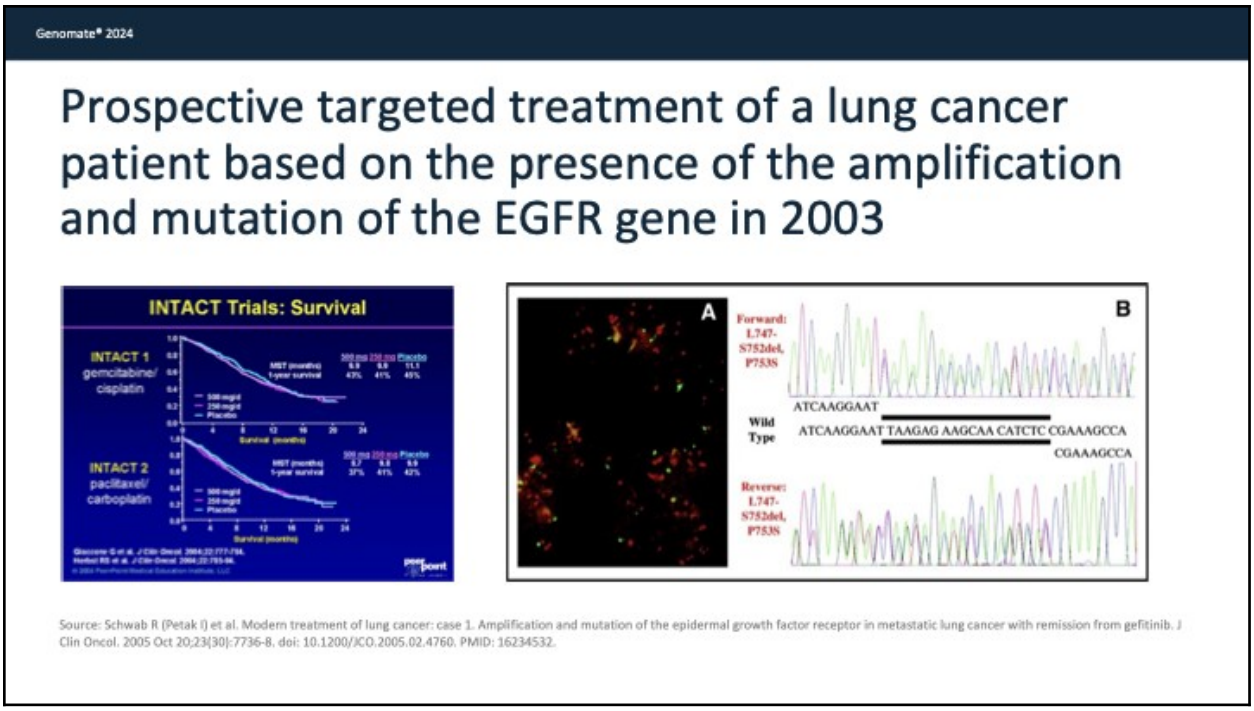
This was very exciting to start to understand the molecular mechanism of the disease. We knew that if we took this fusion gene to transgenic mice (genetically modified mice that have had DNA from another source added to their genome), the mice developed leukemia. We could knock it out and silence this gene and actually stop the cancer cells from growing.

I usually describe it like this feeling that we see the nail in the head that causes the headache. As a young doctor, it was very frustrating to me that we couldn't really target that cause, and we could only use the symptomatic therapy, and then those patients actually had a worse prognosis. Now, of course, fast forward now, we have Imatinib (Gleevec, a type of cancer growth blocker called a tyrosine kinase inhibitor). The good news is that those patients that we lost in 1995 can be cured and saved after 2000, when we had Imatinib targeting this genetic variant.

In 1995 I decided to go into research and went to St. Jude Research Hospital, where we did a lot of research on signal transduction (the process by which a cell responds to substances outside the cell through signaling molecules found on the surface of and inside the cell), regulation of apoptosis (cell death), and cell division. This was to discover the first targets. 20 years ago, we started developing the first molecular diagnostic tests that now we call companion diagnostics to bring this whole dream of “precision oncology”.

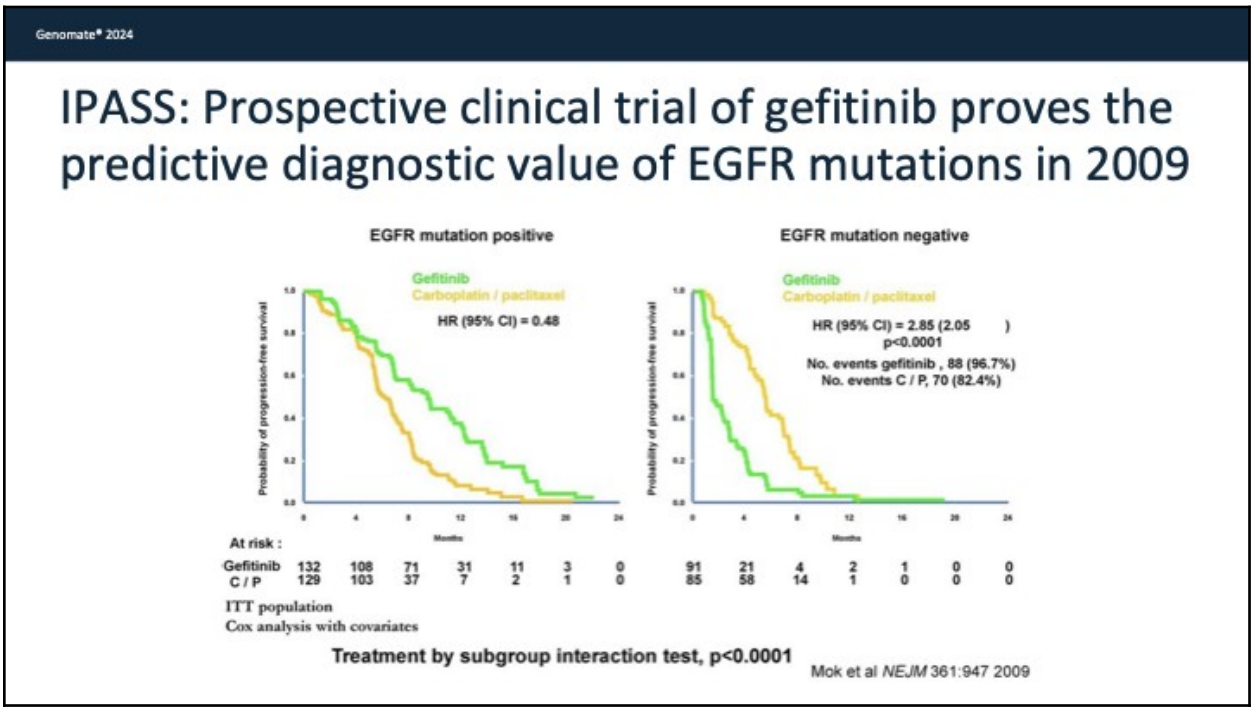
The simple idea is that if you can identify the cause of the malignant transformation, the mechanism and the target, that can be a breakthrough to an effective therapy. In the history of medicine, in many cases, when we understand the mechanism of a disease, we can identify the best solution.

This was the first period of my research and journey towards where we are today.



There was a significant milestone in 2003, when we identified the activating mutation of the tyrosine kinase domain (which functions as an "on" or "off" switch in many cellular functions) of the epidermal growth factor receptor (EGFR, a protein found on the surface of certain cells that helps them grow and survive) in a lung cancer patient. It was more than 20 years ago now. At that time, there was no evidence that linked this genetic alteration to response to a targeted therapy. We didn't really know, we just thought that this patient would benefit. But that year, gefitinib (an oral drug that inhibits the epidermal growth factor receptor tyrosine kinase, which can prevent cell proliferation and tumor growth) was developed to block this target. It just failed in a phase three clinical trial in unselected patients despite the fact that lung cancer cells mostly express this protein, which makes sense, because they derived from the epidermal cells of the lung, that that should be a good target. But at that time, we didn't think about that. Simply having a growth factor receptor on the cell surface of the epithelial or epidermis doesn't mean that it's actually the cause of cancer in that patient. You have to see a transformation or genetic event that makes this tyrosine kinase receptor that originally has the function to regulate self growth to be independently activated. We saw that in this patient in the cancer cells, it was not just expressed, but had the activating mutation and expression, and amplification of the gene. We requested an investigator-initiated clinical trial. We were really happy to be able to obtain the drug for this patient, although we had to fight for it, because the ethical committee just said that we have the highest level of evidence that it should not work based on the phase 3 trial. We had to argue that there was a reason why we thought that this patient was an exceptionally good candidate for this drug, because there is a “nail” we see in this tumor. This patient had an amazing response, a complete remission, and disappearance of the brain mets (metastases) and lung mets and lived for more than five years and died of unrelated causes.

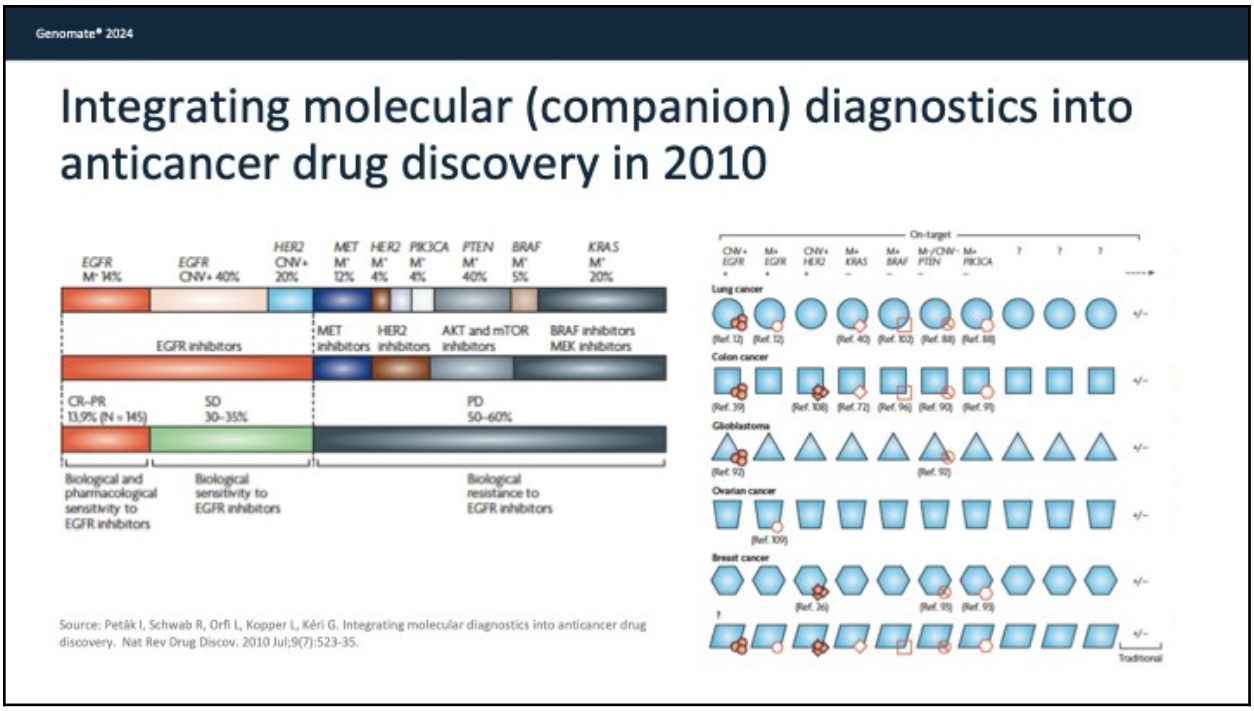
That was really a transformative moment in my life, to see that the concept actually works.



We had to wait until this drug, gefitinib, was approved for these patients because we had to wait for randomized clinical trials with four arms that actually stratify patients based on the presence of the genetic alteration, the biomarker, and they had to wait for the results, how they responded to chemotherapy versus targeted therapy. But of course, this was only possible because this gene was frequently mutated in the Eastern Asian patient population.

We had the concept that we have to prove the predictive efficacy of these biomarkers in randomized trials.

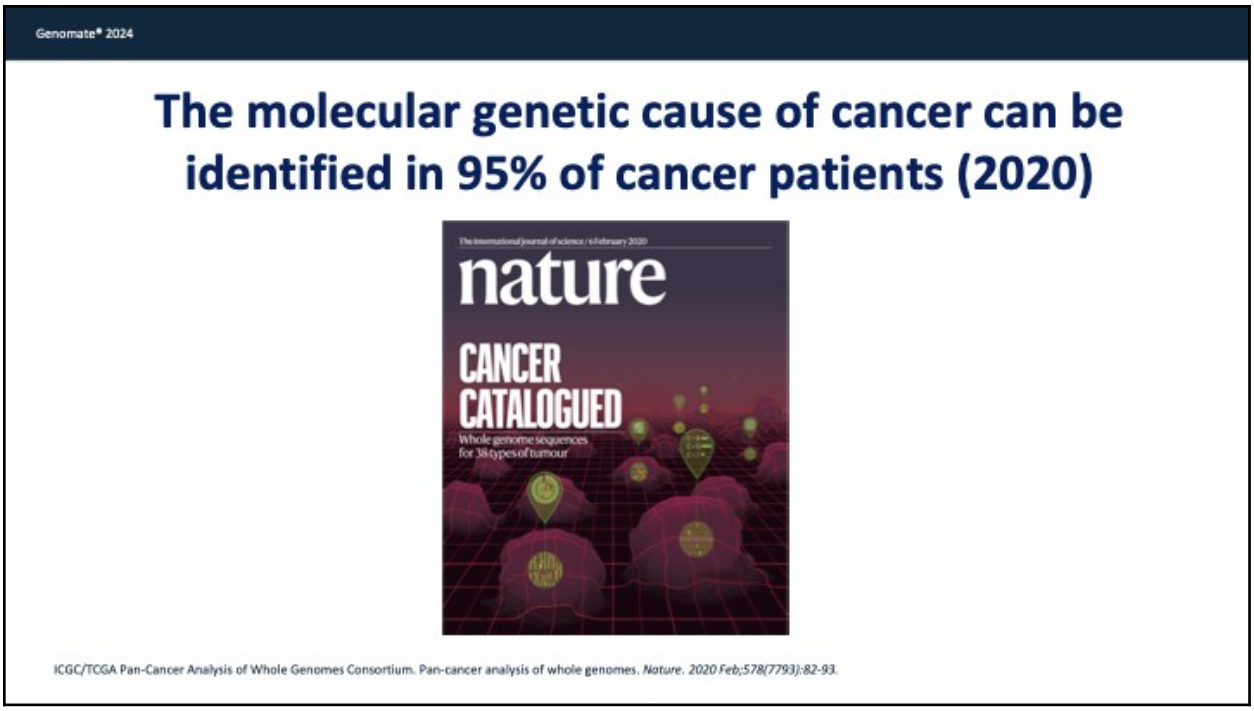
“Matching Patients with Treatments” (Istvan Petak, MD, PhD) [#107]



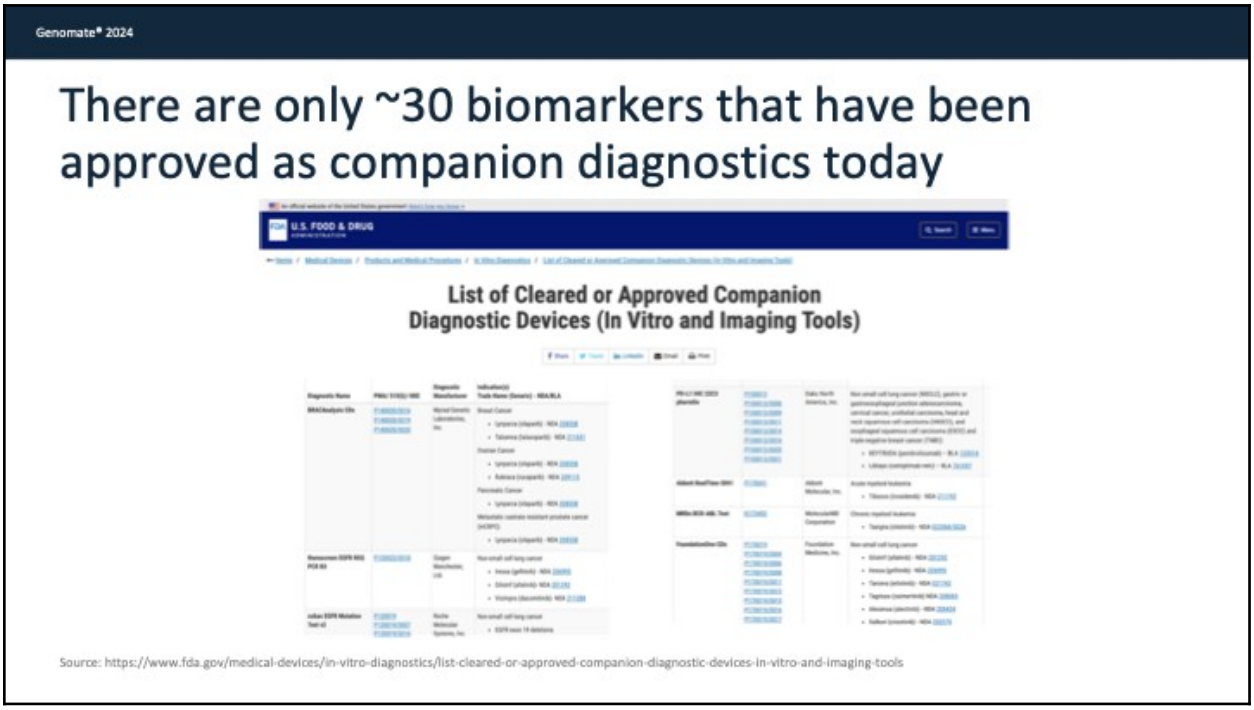
That's statistically true. It became obvious that it's extremely cumbersome as the number of these genetic alterations was growing, and multiple genetic alterations cause the same disease, like lung cancer or any cancer. We realized that one can have one oncogene or driver gene that can cause different types of cancers, and one type of cancer can be related to multiple different genetic alterations.

We had a review in 2010 on this topic, and predicted that all targeted therapies need a companion diagnostic test. This is how we will get there. We already thought that we would need tumor-type agnostic therapies, because if the molecular-targeted therapy targets a driver gene that occurs in multiple cancers, it makes more sense to register them according to the target.

“Matching Patients with Treatments” (Istvan Petak, MD, PhD) [#107]

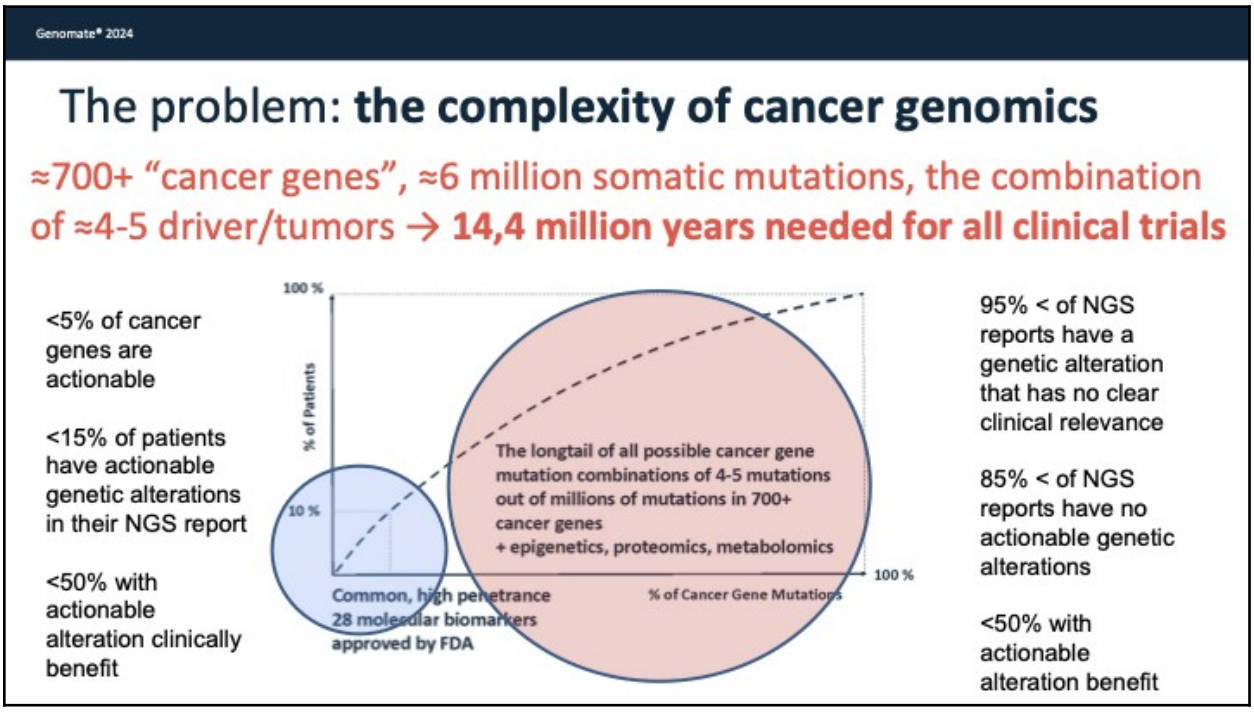


Fast forward to reality in 2020. This is exciting, because in this beautiful large research paper published in Nature in 2020, the whole genome sequencing consortium reports that were based on whole genome sequencing data could identify the genetic cause of cancer in 95% of cancer patients. We are in a post-cancer genomic era. That's really exciting. We should be able now to exercise the concept of precision oncology, targeting driver genes in every cancer patient.



“Matching Patients with Treatments” (Istvan Petak, MD, PhD) [#107]

When we look at the number of companion diagnostic tests or targets and biomarkers approved by the FDA as a predictive biomarker, the number is around 30. This is really low. This is really frustrating, because this means that only a fraction of the patients actually have a biomarker that can be used as a companion diagnostic. There is slow progress here.



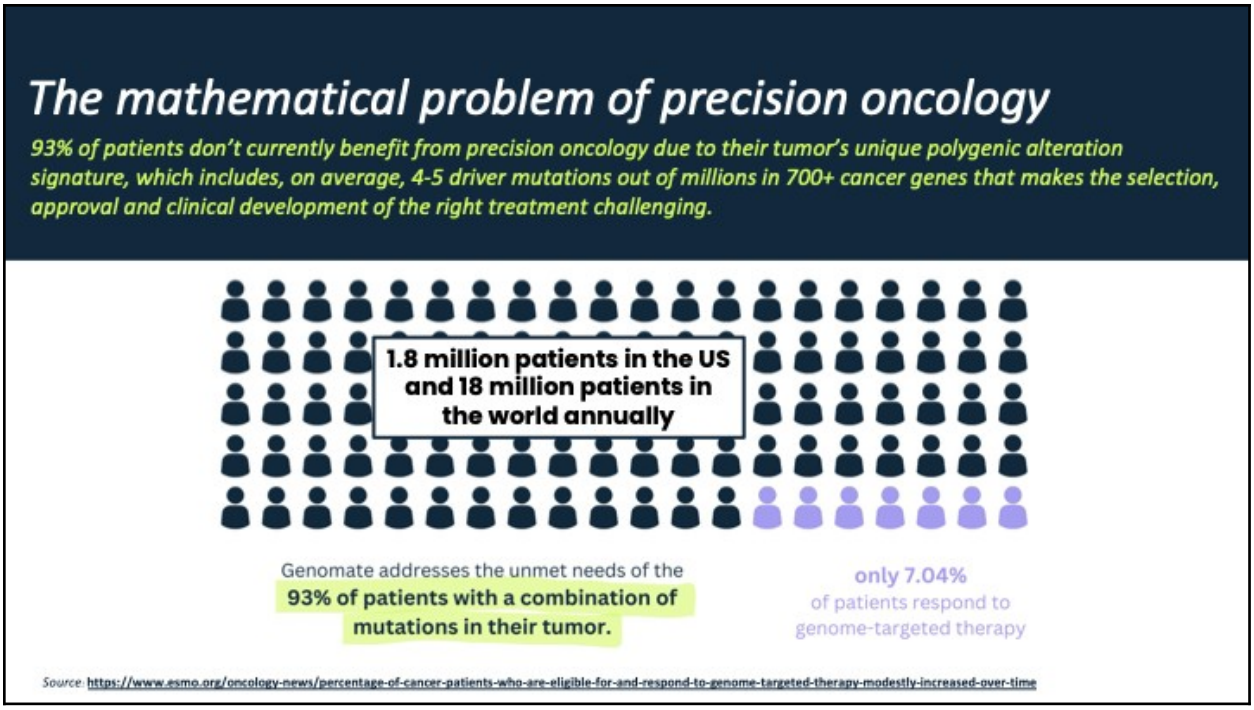
The reason is a simple mathematical reason: now we know that the number of human genes are countable. It's not infinite. Also the number of cancer genes is countable. We know now that we have around 700 cancer genes, and the number of new genes we discover gets less and less as we saturate the number of genes discovered. The problem is that 700 is more than 100. So the average frequency is less than 1%. And on top of that, each gene can carry multiple different mutations. And on top of that, each cancer carries a combination of four or five mutations, between two and twelve. The good news is that there is also a logical limit to how many mutations we have. From Professor Vorgestein, we learned the history, and it seems to be true, that we have only one genetic alteration per signal transduction pathway. So therefore, the number of signal pathways limits the number of drivers.

Because of the long tail distribution of these driver genes, we have more frequent and less frequent and also the combinations have a distribution of more frequent and less frequent, and of course, logically, in the past decade or so we were able to concentrate on the more frequent genetic alterations and combinations of genetic alterations to develop drugs and companion diagnostics, but it's getting harder and harder as we move and we try to cover more patients.

This is why today, we thankfully have molecular profiling assays routinely used, and we can easily sequence all the genes or hundreds of genes, but only a fraction of these genes are

actionable, if we define actionability based on being an approved companion diagnostic biomarker.

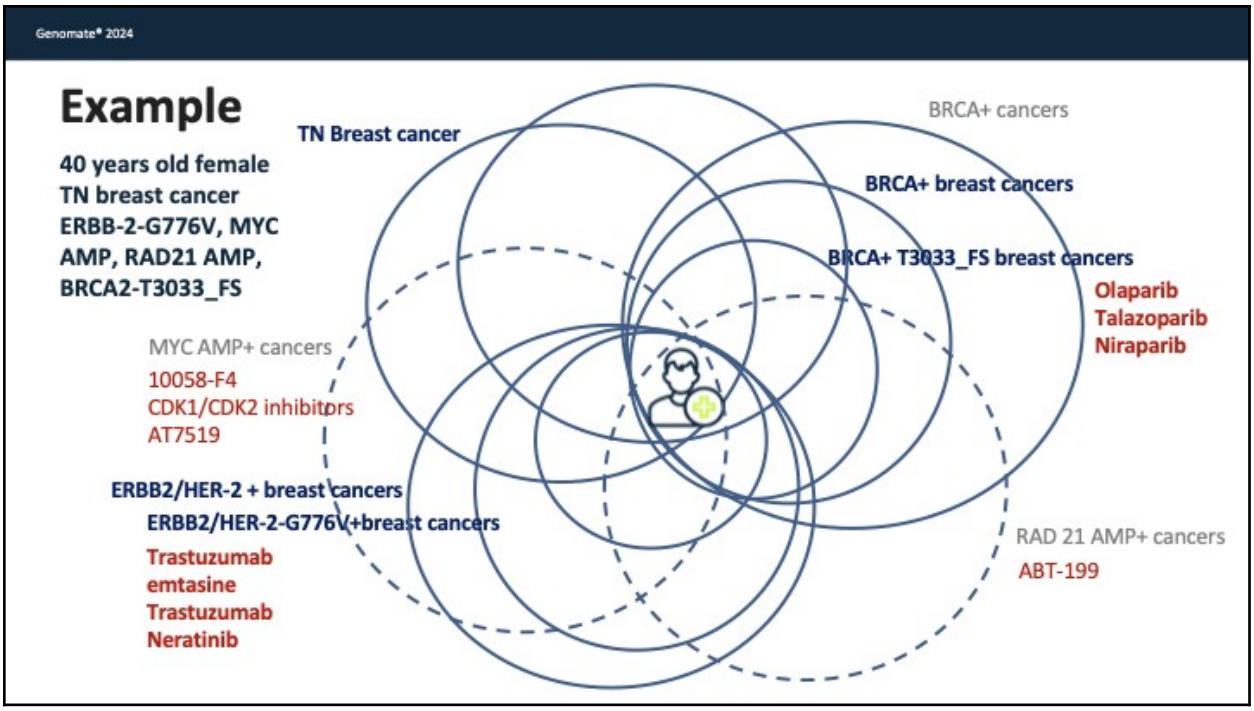
Although many reports identify the genetic cause of cancer for that patient, it's not really actionable for the doctor. Even those who have an actionable biomarker, it’s not sure that they would respond, simply because one of the very obvious reasons is that the co-occurring other mutations can alter the response to a therapy that actually targets one out of the five therapies. If there are multiple, we don't know which one to choose.



This is why only a very small fraction of patients today actually benefit from this very straightforward concept, what we call precision oncology.

This is something really frustrating after 20 years, and now that we can easily develop new targeted therapies, and we already have 200 and we have the diagnostic technologies to identify these mutations.

“Matching Patients with Treatments” (Istvan Petak, MD, PhD) [#107]

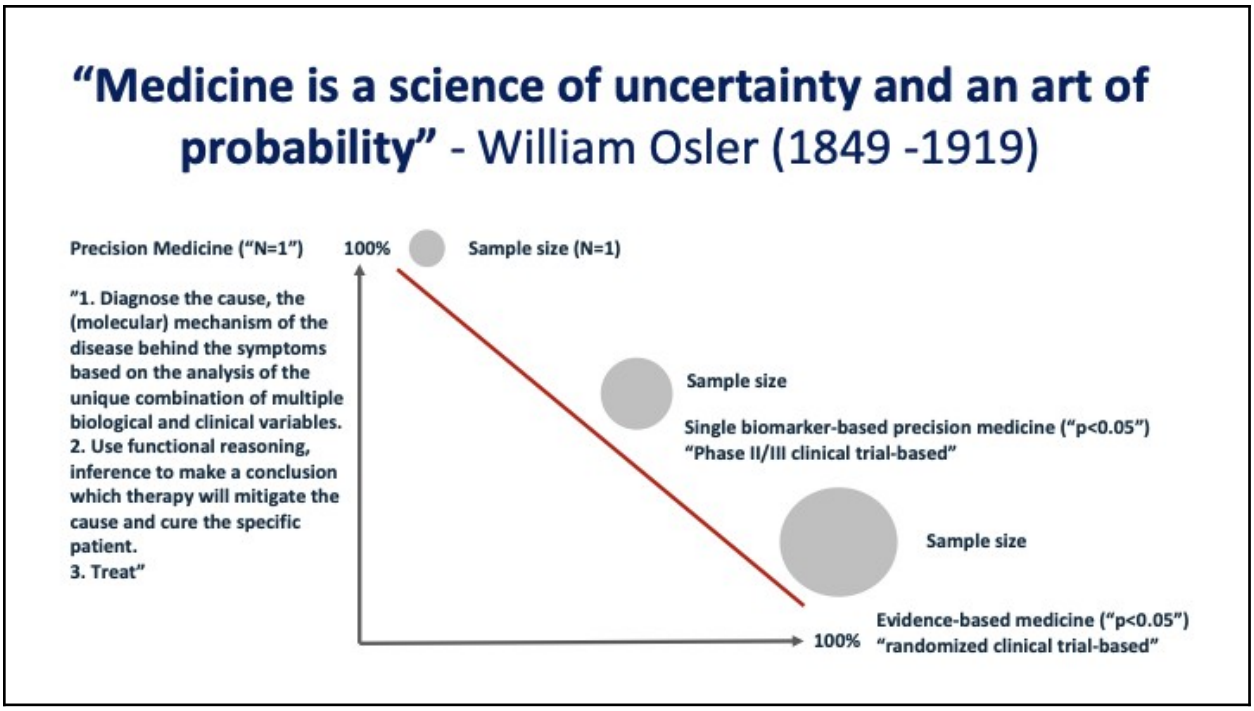


To give you one very simple example in clinical practice, if there is a breast cancer patient, in this case, we know that breast cancer patients who carry the BRCA mutation can be eligible for PARP inhibitor therapy (poly ADP-ribose polymerase inhibitors, a type of targeted cancer drug that blocks a protein for DNA repair, preventing cancer cells from repairing their damaged DNA, which can cause them to die) because this is registered for BRCA mutants. We also know what to do with HER-2 positive (human epidermal growth factor receptor 2, a protein that promotes the growth of cancer cells) breast cancer patients because there are inhibitors approved for HER-2 positive breast cancer patients.

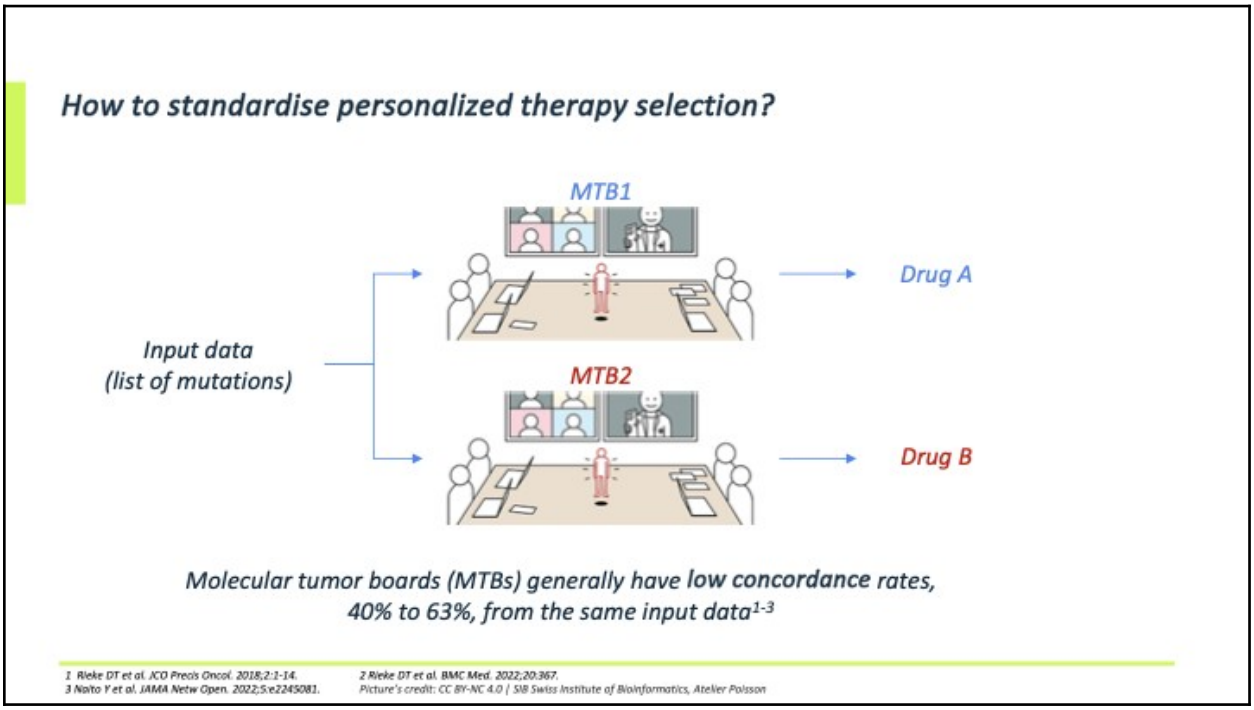
But we are still waiting for any trial that compares HER-2 inhibitors and PARP inhibitors in the subpopulation of patients who have a BRCA mutation and are also HER-2 positive, and so on and so on. If you imagine these multiple groups, then we see that the patient is in the intersection of multiple biomarkers. So the question is: what is the best therapy for this patient?

Theoretically, we would need clinical trials that compare different options for this patient. But as on my previous slide, I showed that I made the calculation that we would need 14.4 million years to figure out and do all the clinical trials to prove which therapy is the best for this patient.

“Matching Patients with Treatments” (Istvan Petak, MD, PhD) [#107]

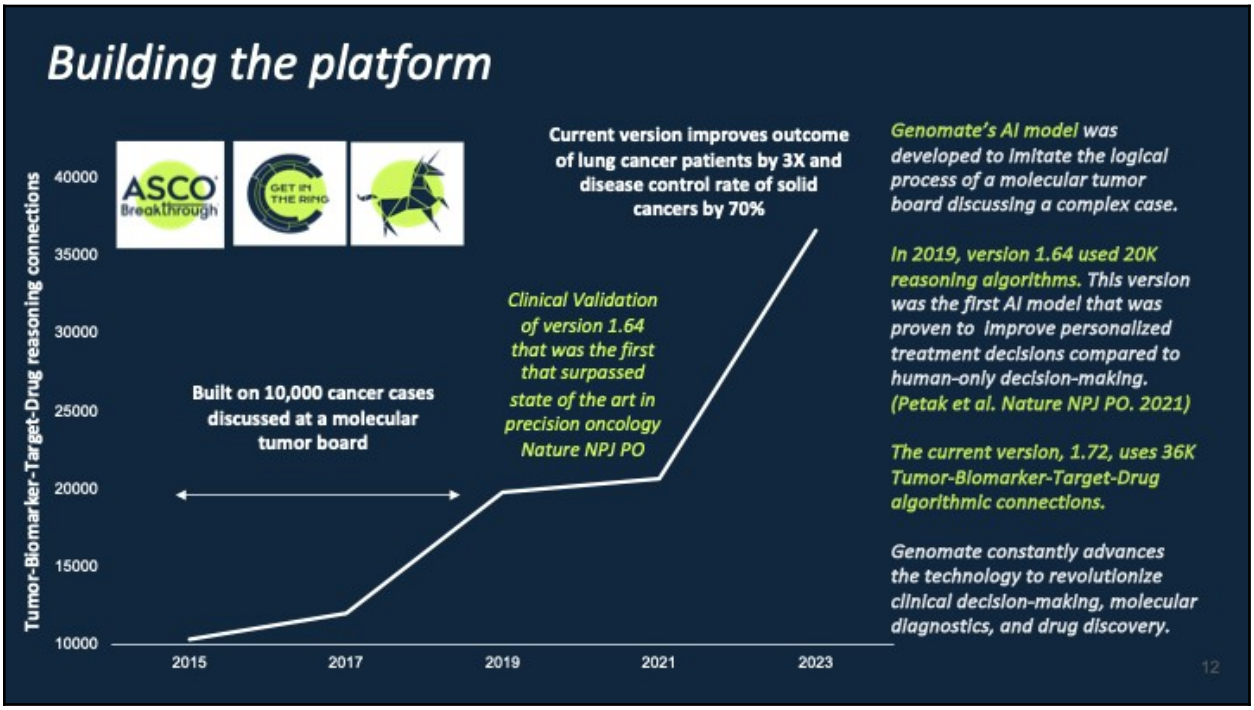


This is just a general problem of the concept of personalized therapy: how to combine the concept of personalized therapy and evidence-based medicine. We want statistical evidence that what we are giving to our patient is the best possible therapy.



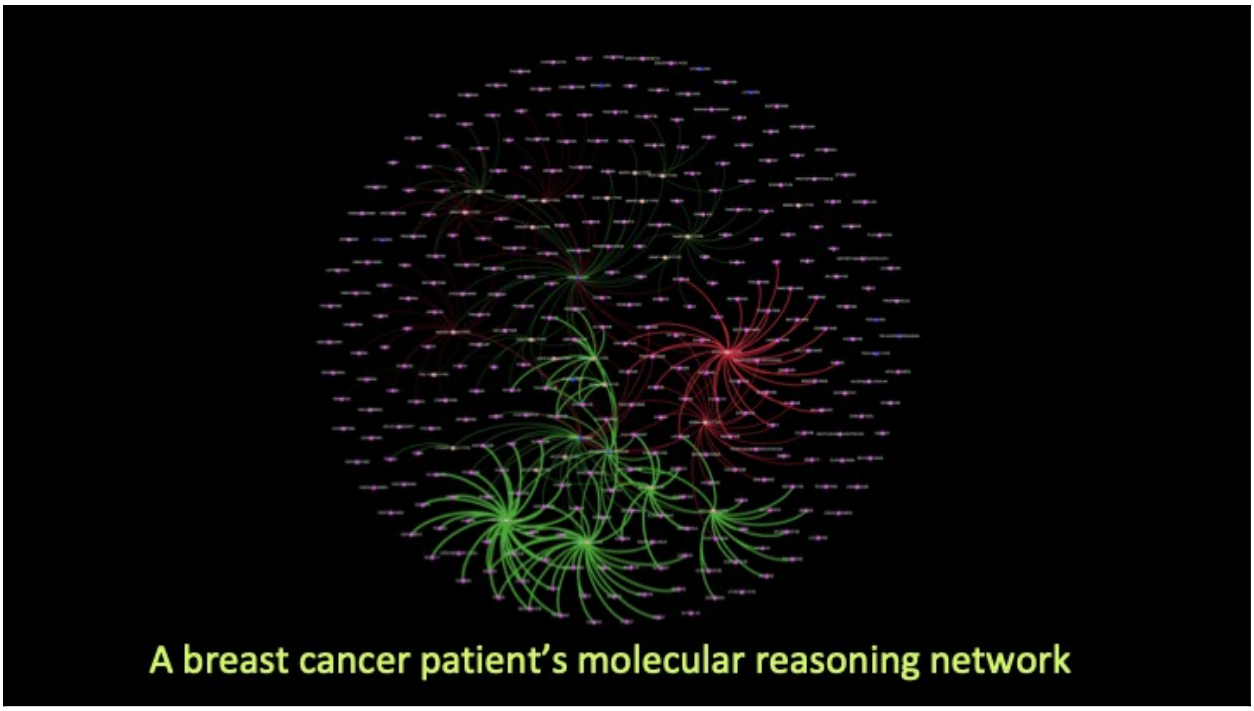
We are trying to develop a solution beyond what we already have, such as molecular tumor boards. Because that's the practice today when we want to go beyond the companion

diagnostics, and we want to consider other mutations in the patient and use it to design a more personalized therapy or target an off-label therapy, or are referring the patient to a new clinical trial of a new targeted therapy. But the problem is that of course, it's extremely difficult to scale and provide it to all patients. It's very subjective and the concordance between the opinions of molecular tumor boards if you send the same results and molecular diagnostic test results to two boards is only 44%, based on studies.

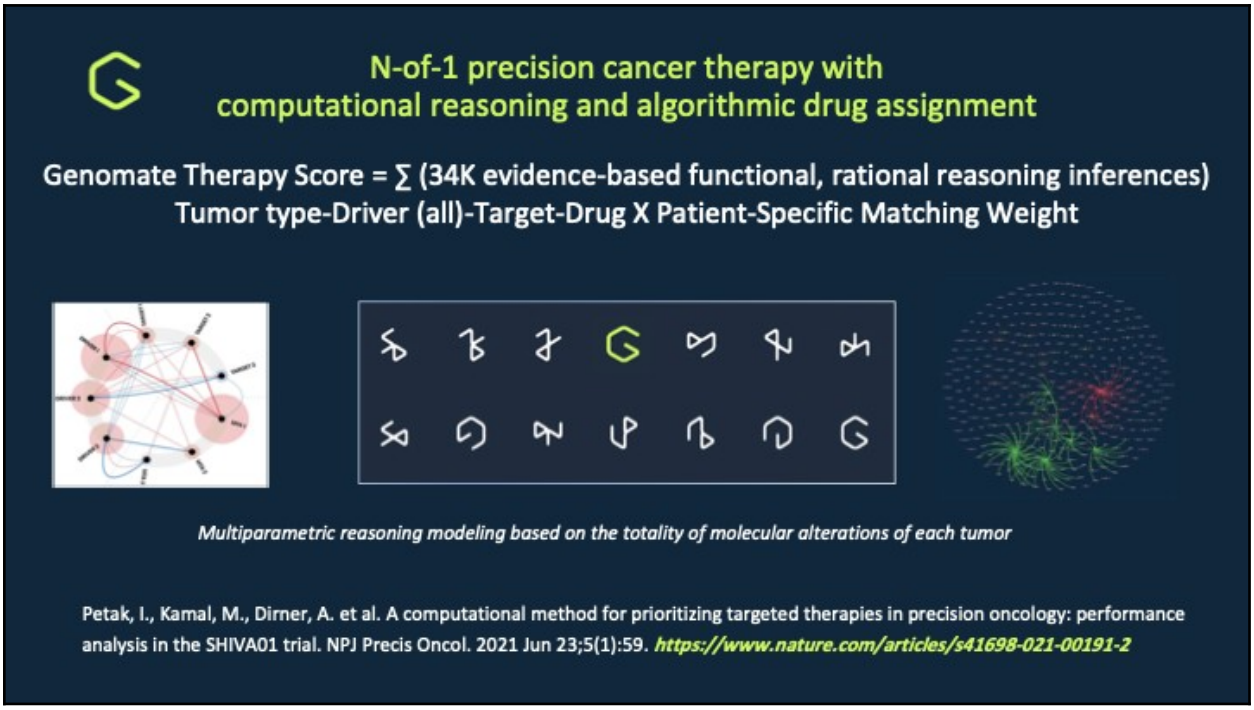


In our case, we also did a molecular tumor board analysis for 10 years. We analyzed 10,000 cases, and we tried to build the best logical mathematical model, how to combine information about each genetic alteration we found in that patient. The question was if we can build a mathematical model that is synced or the best mathematical algorithm how we combine information that links one driver gene to a possible molecular target and to a targeted therapy in a network because in reality, this is a network problem, where each gene can be linked to multiple targets and each target can be linked to multiple targeted therapies, and each target and targeted therapy can be linked to multiple drivers in the same patient.

“Matching Patients with Treatments” (Istvan Petak, MD, PhD) [#107]

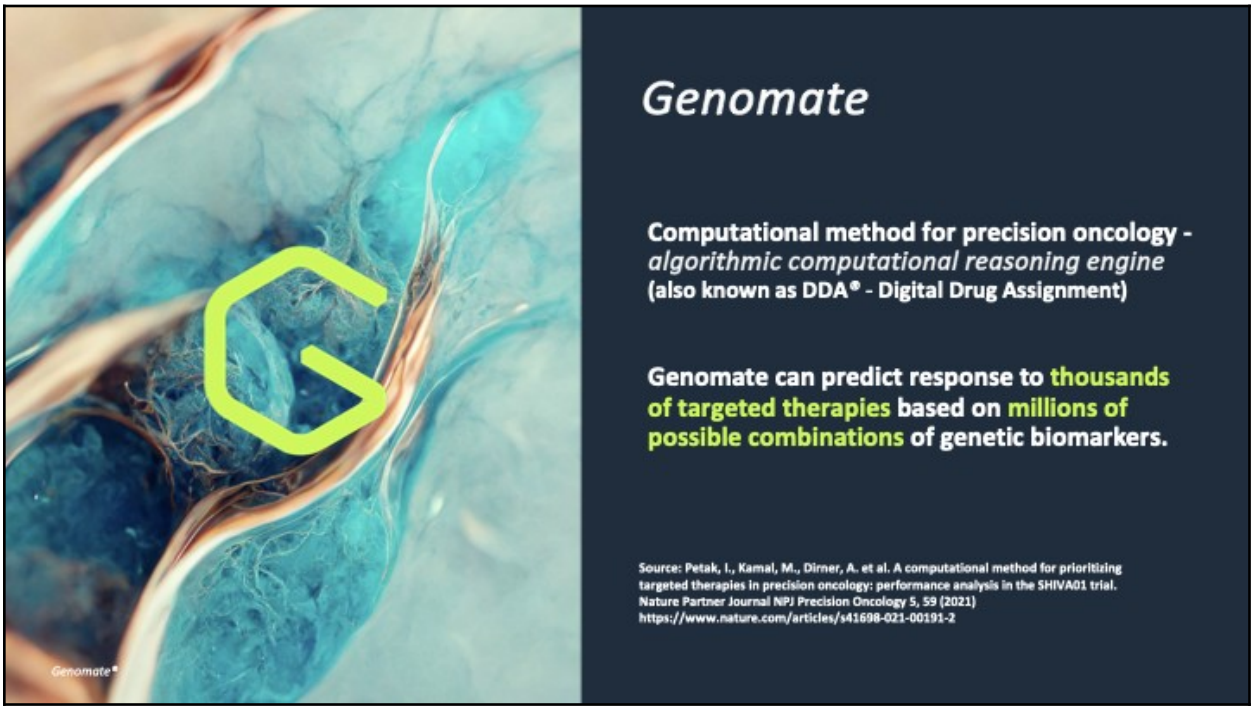


This is how it looks if we visualize a breast cancer patient case where you have five driver alterations that are positively or negatively associated with different targets and treatment options. Here in this model, you can see that the strength of the link is represented by the thickness of the lines. The green lines are the positive associations, and the reds are the negative associations.



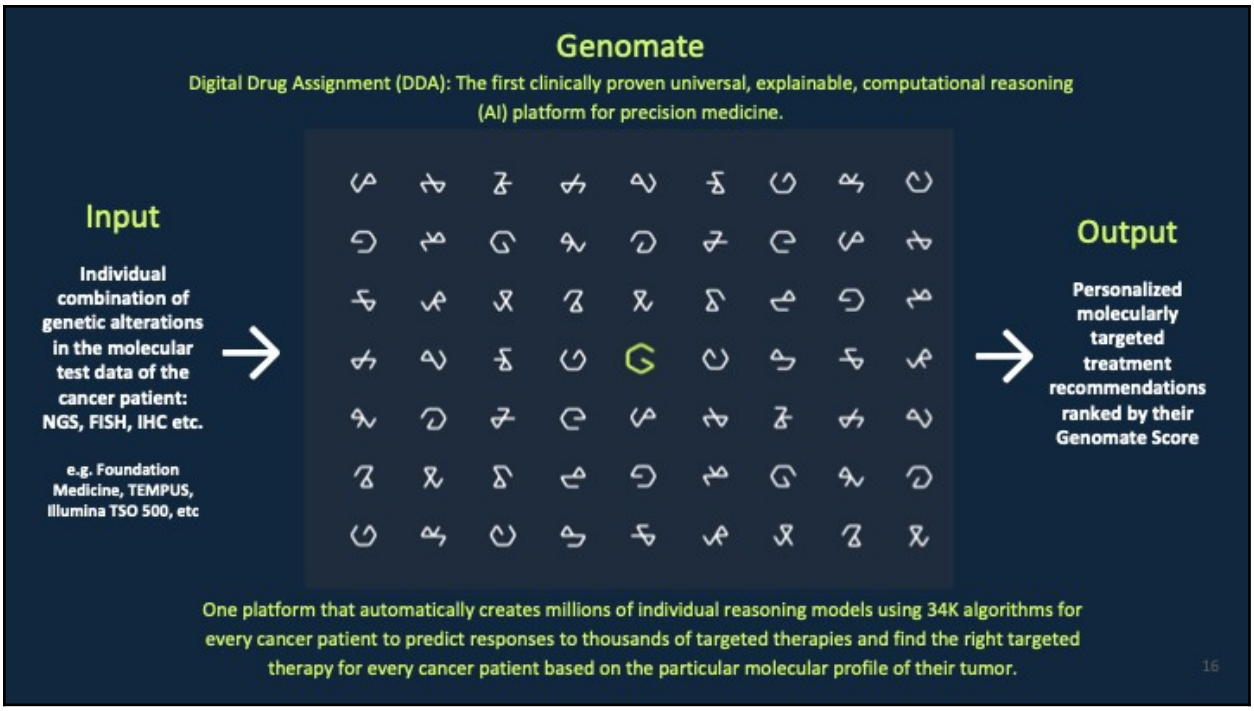
“Matching Patients with Treatments” (Istvan Petak, MD, PhD) [#107]

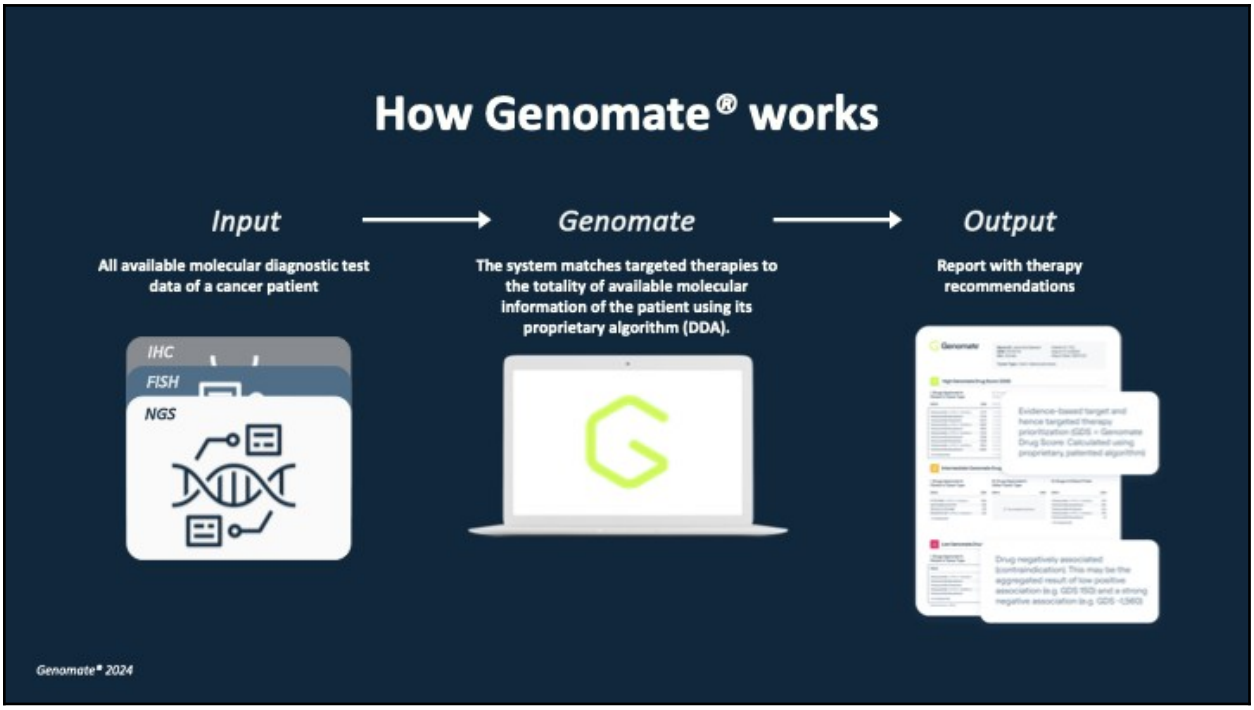
Overall the logic of the mathematical solution is to combine all of what we know about the general genomic profile of the patient in a logic where we give a weight to each piece of information based on the similarity of the characteristics of the patient and biological purposes between the patient and the subjects studied in that clinical trial that was used to generate that conclusion, that reasoning, that functional link between the genetic alteration and the target in the targeted therapy, and create a unique model for every cancer patient based on the unique characteristics of each patient. We have a universal model, but we have to generate a unique model for each patient to do this. This method actually is aligned with guidelines of ASCO and ESCAT.



This is what we developed. We call it a computational reasoning system, or algorithmic method, to select the right targeted therapy for every cancer patient based on the individual molecular profile of their tumor, based on the individual combination of mutations of that patient, and to predict whether any targeted therapies, targeting one out of the five, or cancer genes on any target that are linked to any of these targeted therapies that can work.

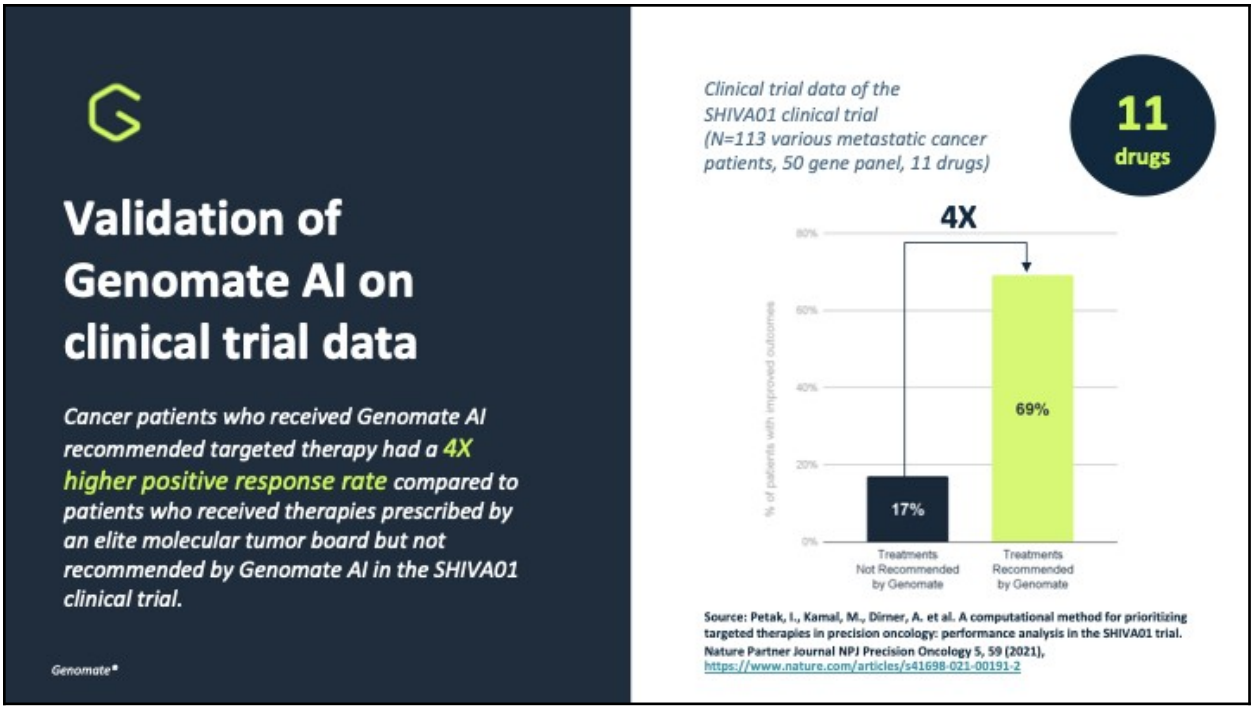
“Matching Patients with Treatments” (Istvan Petak, MD, PhD) [#107]





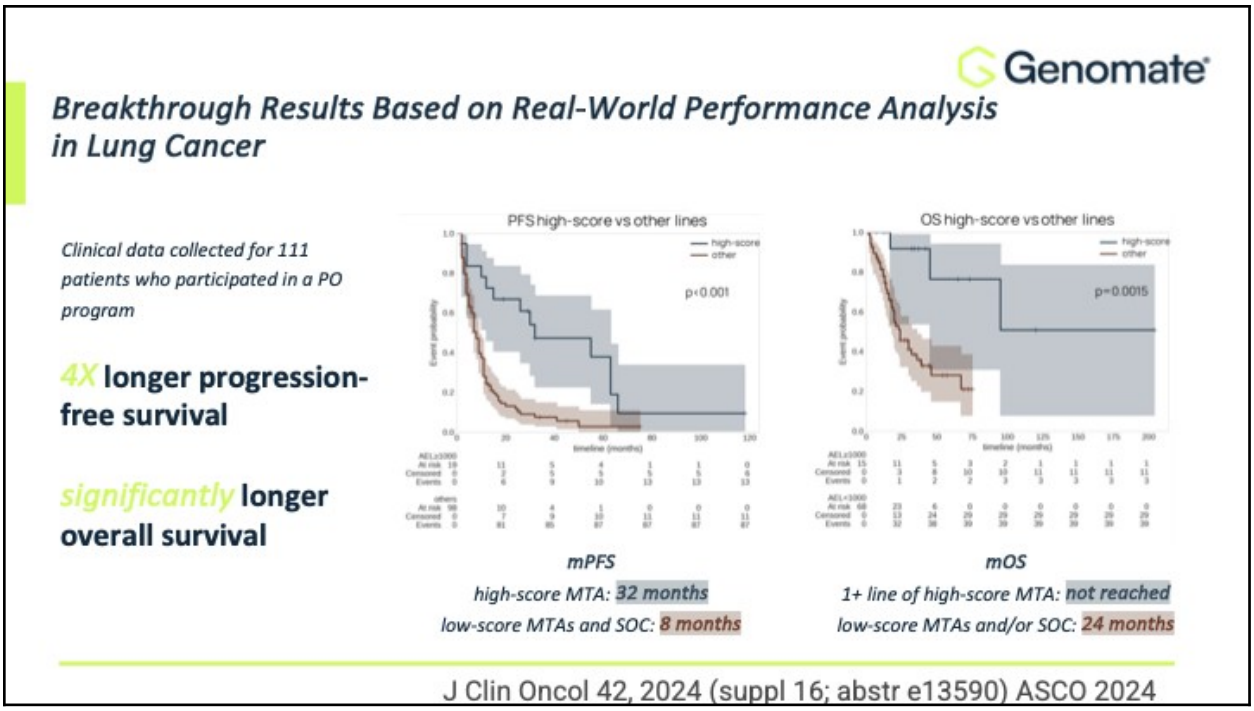
We concentrated on the real world, clinical practice, and data that is already available for most cancer patients. Now, luckily, more and more patients actually have an NGS (next generation sequencing) test, and immunohistochemistry. As input, we use only test results that are readily available for most patients. You don't need a new test. Typically what we need is the results that the most patients already have in their medical records. We use our algorithm to generate a

score for every possible targeted therapy. Then we rank them according to this score. We group them in tiers of highly positive, intermediate, and low.



Of course, the question is: does it work? That's the most important thing. It was exciting when we worked together with Institut Curie. We analyzed the data of SHIVA01 that was the first randomized precision oncology trial, led by Christophe Le Tourneau. In this trial, patients were treated based on their molecular profile, and with one of 11 different drugs. The tumor board predetermined which targeted therapy to use in the presence of which driver alterations or biomarker. When we received the molecular data, and we had to predict with our model who would respond to this therapy, we found a 4x difference between patients who received this in terms of response rate and also significantly difference in PFS (progression-free survival) between patients who received the therapy, also supported by the model, compared to those who received the matching therapy based on the presence of a molecular target that was not supposed to support that model.

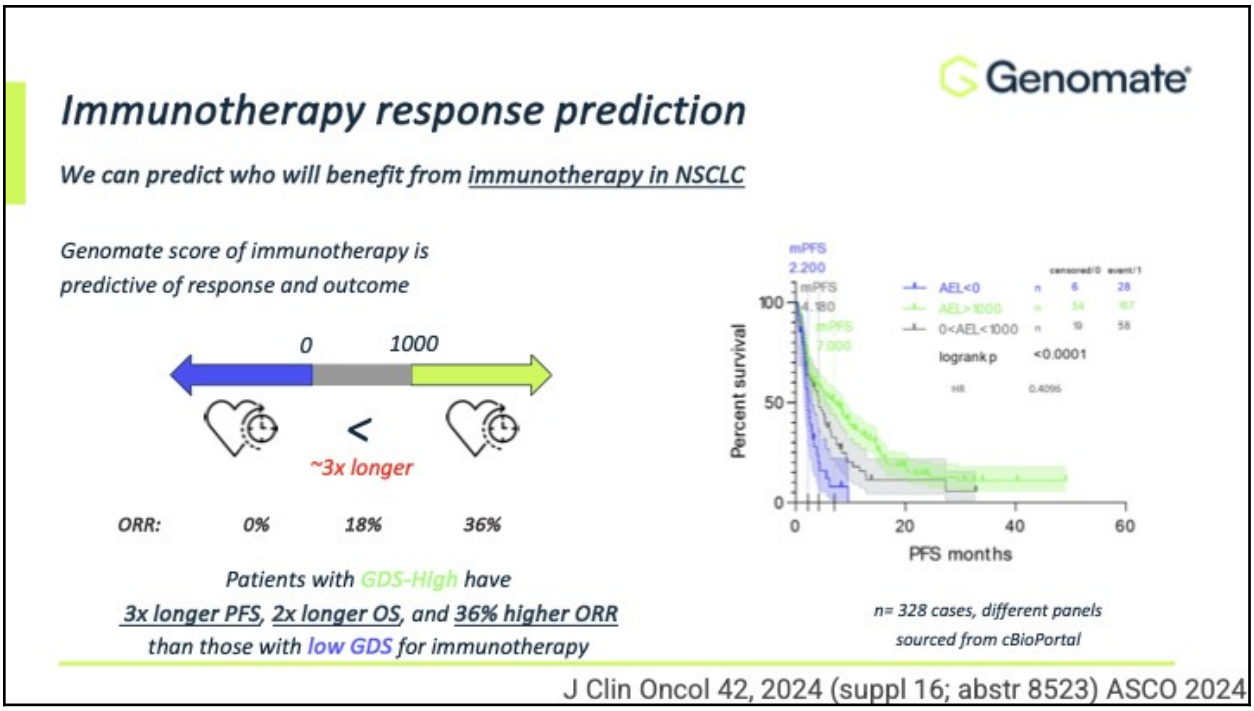
It was exciting that we could see that a computational model can improve treatment decisions by computing in all the genetic alterations, instead of making a decision based on the single alteration. Because we have a limited number of cancer genes, using information from the totality of the five genetic alterations, instead of making a decision based on a single alteration, really improved our predictive capabilities.



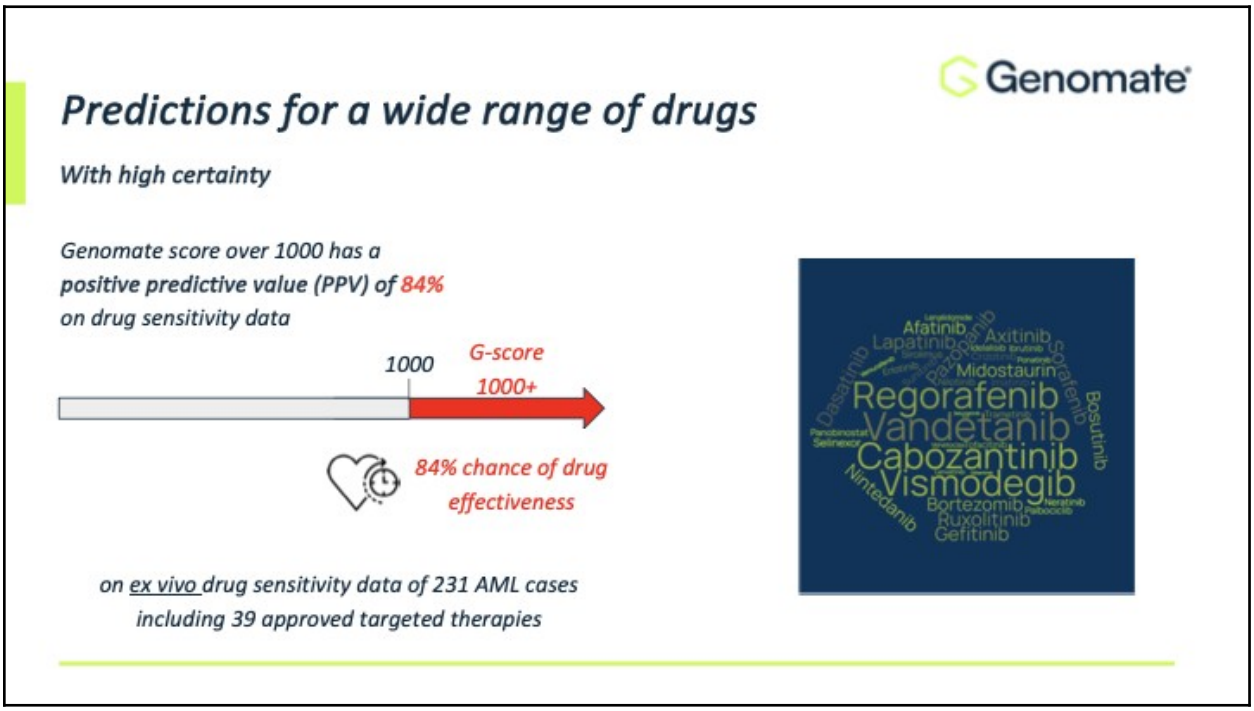
Jumping to 2024, we were at ASCO this year, a few weeks ago, where we had two abstracts, one poster, where we showed our real world data, where we showed that lung cancer patients in real world who received a therapy that had a high predictive score generated by the model had not just a better response rate, but much, much longer progression free survival and overall survival. It shows the power of this concept that I tried to start to work on 29 years ago, and we and a huge community of scientists are working on, that if we can select the right targeted therapy based on the what we know today about the molecular profile of the patient, and in the functional, biological background of the cancer, we can achieve such good results.

I want to emphasize that this improvement in survival is achieved simply by selecting the drugs that are better matching based on existing molecular diagnostic tests, without the need of any new tests, and without using any new therapies. It's using what we already have in a better, smarter way. That makes me very excited.

“Matching Patients with Treatments” (Istvan Petak, MD, PhD) [#107]



We can also do this with immunotherapies. That's very relevant today. Using the molecular alterations present in the NGS, we can better predict who will benefit from immunotherapy and who will not, and to support treatment decisions. For example, in lung cancer, whether immunotherapy should be used first line, should be combined with chemotherapy, or not.

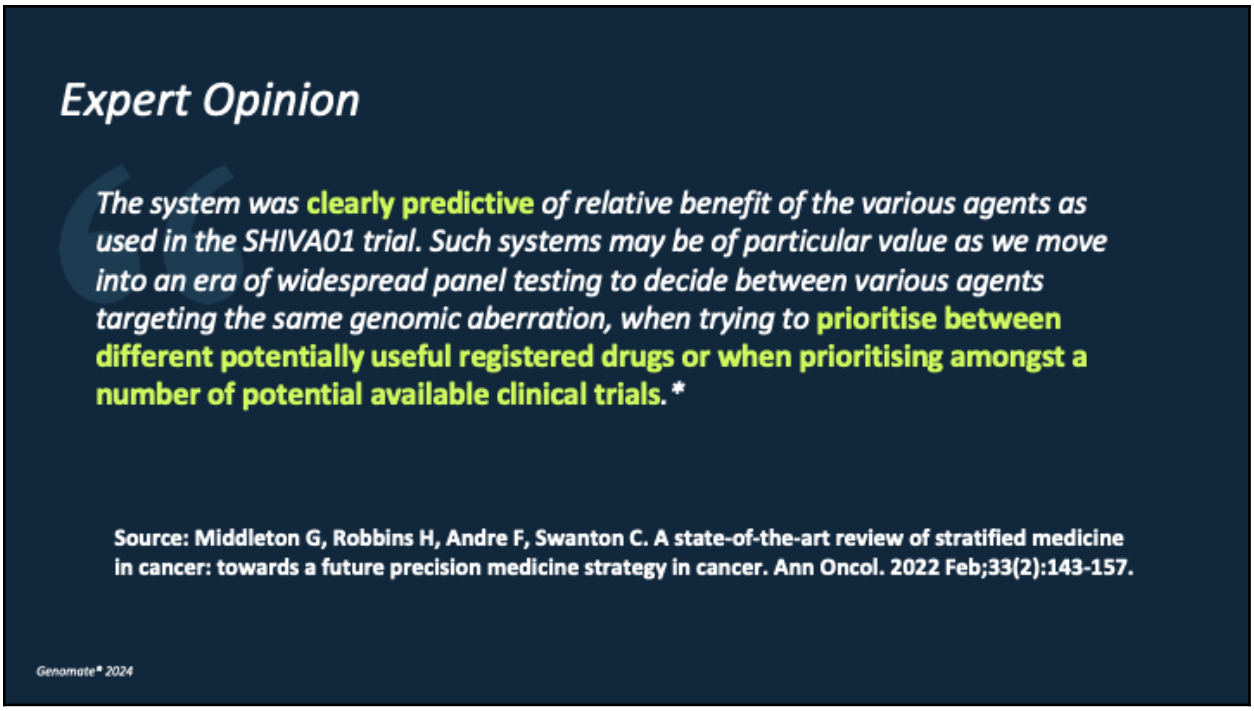


“Matching Patients with Treatments” (Istvan Petak, MD, PhD) [#107]

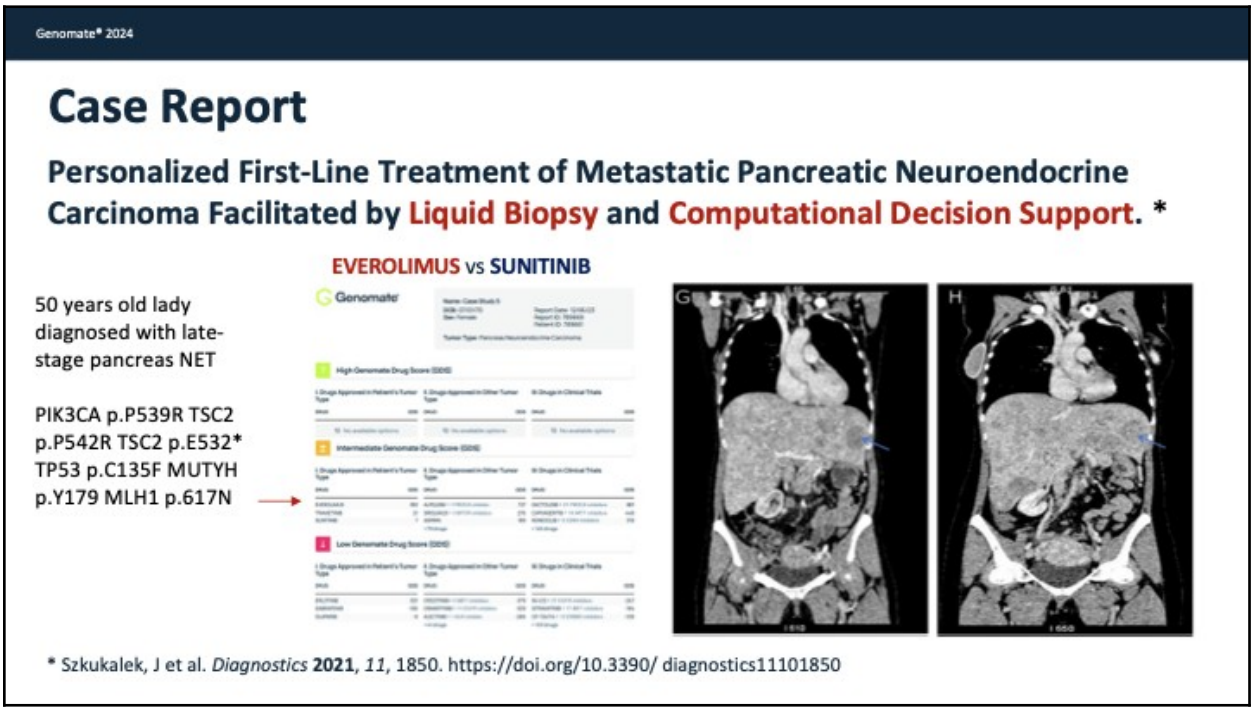
We reproduced and validated the results in multiple data sets. That's the same stat; we have a very robust model in multiple tumor types in multiple models.

That's really exciting because the investigator of the SHIVA01, Christophe Le Tourneau, said that we have a new tool. The software becomes the new device. We need to implement the real concept of precision oncology and solve the paradigm that we want to provide personalized therapy, and we want to select the targeted therapy based on the molecular profile of the patient. But we want to do this in a way that is evidence-based. The only way to do this is to validate the method we use to choose a personalized therapy.

“Matching Patients with Treatments” (Istvan Petak, MD, PhD) [#107]

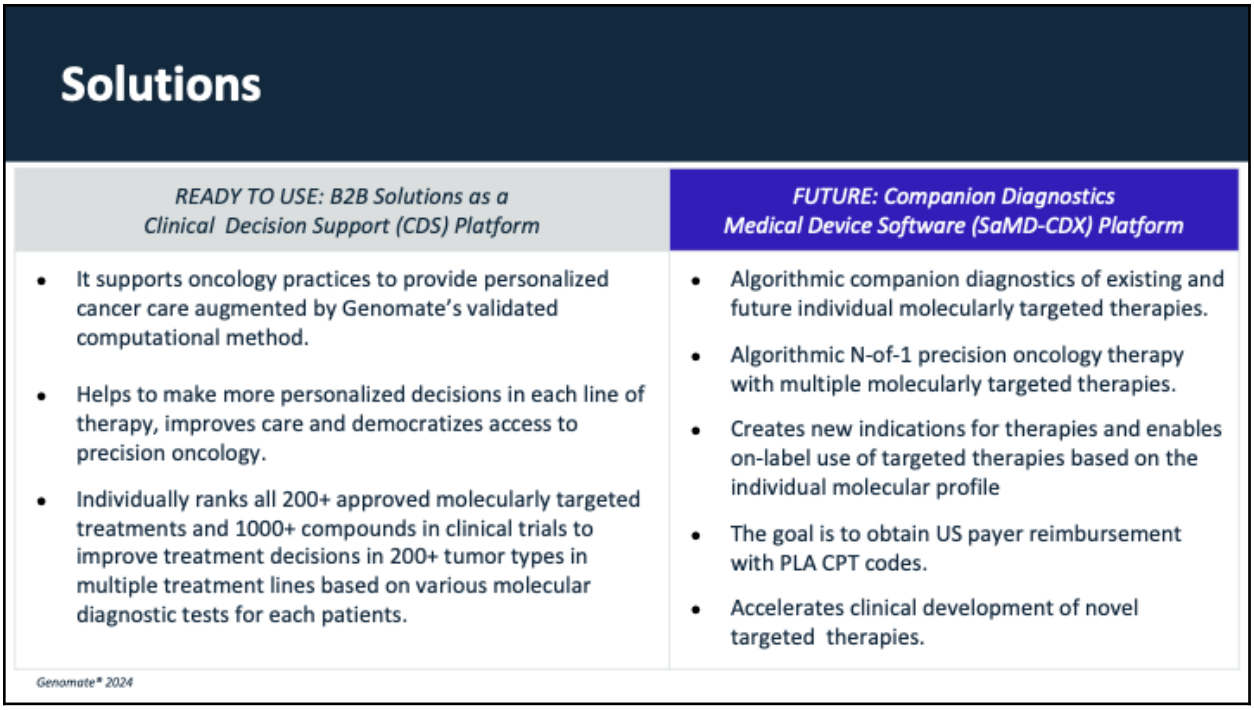


This was also echoed by other key opinion leaders in a review paper citing our paper.



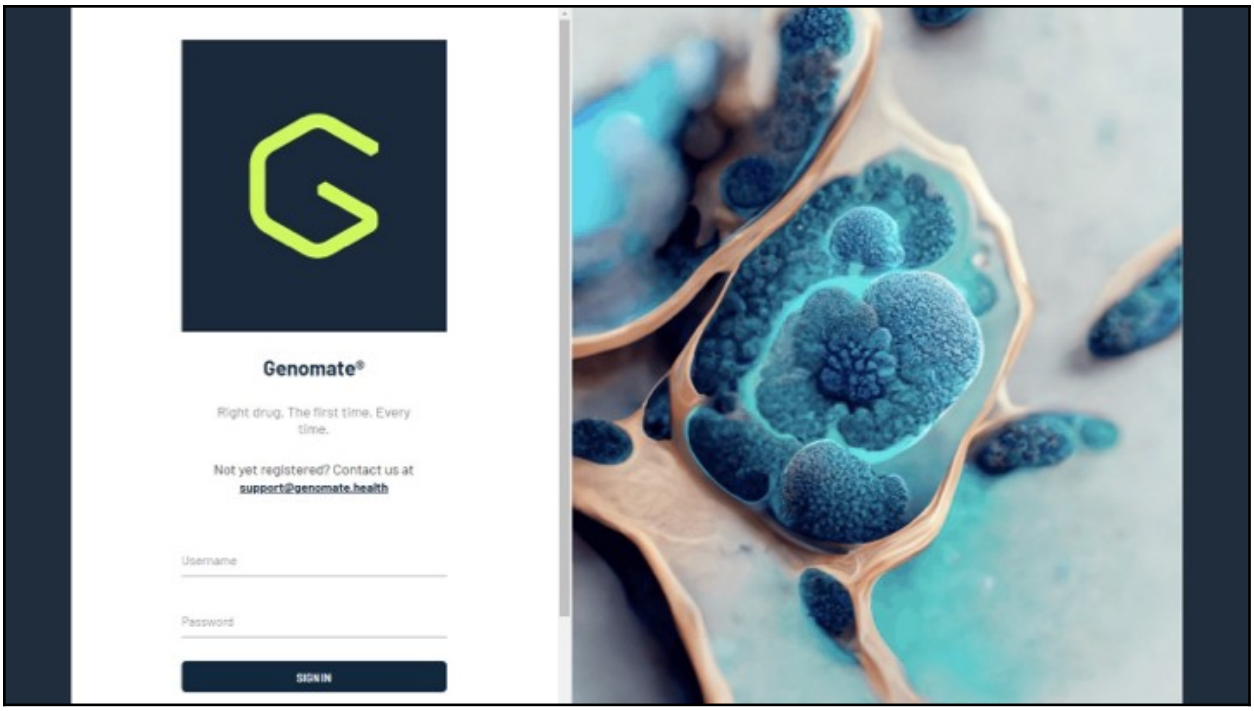
One example of how this can be implemented into clinical practice to support better decisions: This was a first line therapy for a neuroendocrine tumor. It was a very important patient for me. I knew her. She was diagnosed very late with multiple liver mets (metastases). The oncologist had to make this difficult decision of which therapy to choose as a first line therapy out of

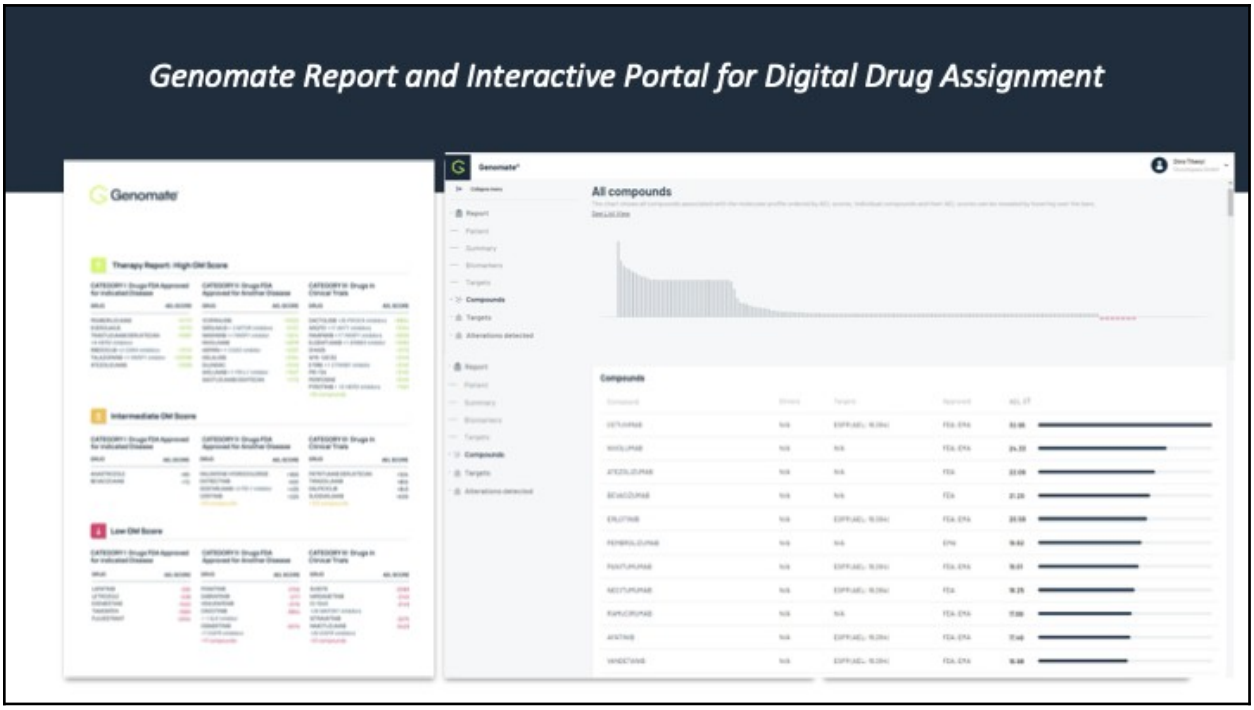
possible registered therapies. We have to realize that for most cancers, we have multiple treatment options already registered because we don't have time to do all the randomized trials and head-to-head trials. So there are multiple options. But we can improve this decision, in which you want to choose, for example, in this case for this patient, based on the molecular profile of the patient and using the model.



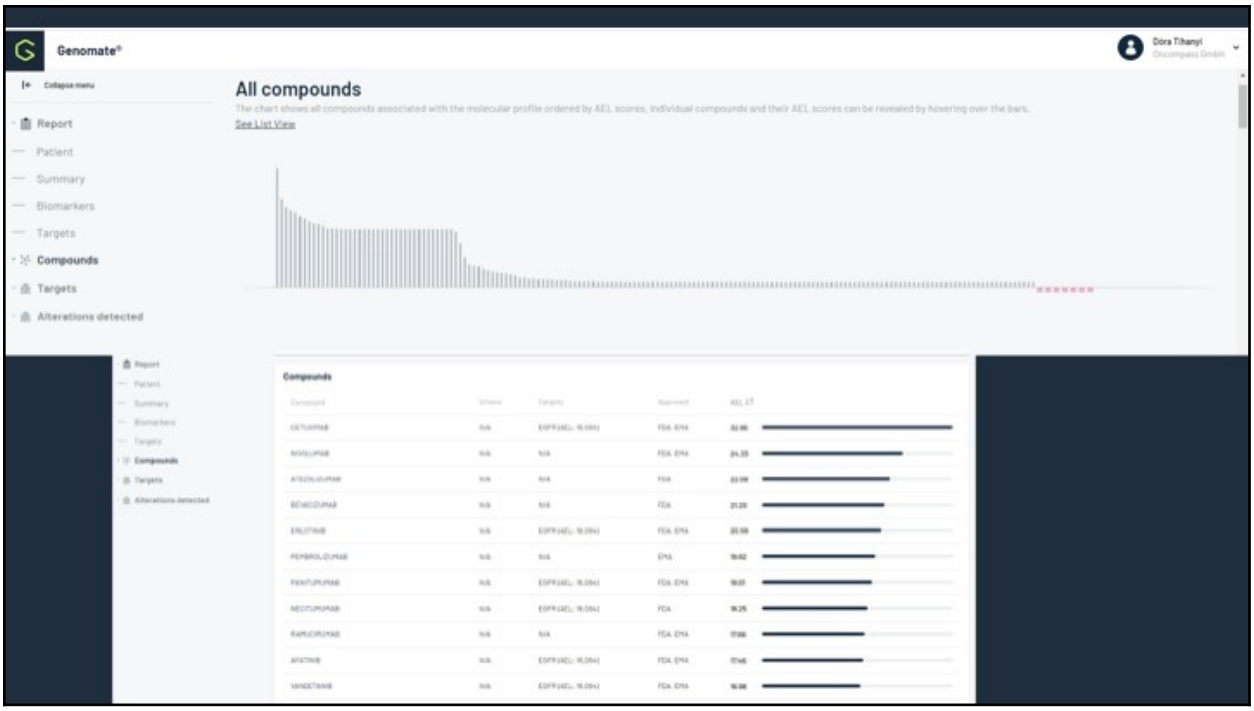
What we want to achieve now is to empower clinical practices to provide better personalized therapies and better personalized treatment decisions. We also want to use this platform to enable oncologists finally to practice precision oncology, so they should be allowed to use a targeted therapy (in the future) based on the molecular profile on label. That would require the regulatory approval of the system as a companion diagnosis and not just the clinical decision support to support better decisions between treatment options already available today.

“Matching Patients with Treatments” (Istvan Petak, MD, PhD) [#107]





“Matching Patients with Treatments” (Istvan Petak, MD, PhD) [#107]

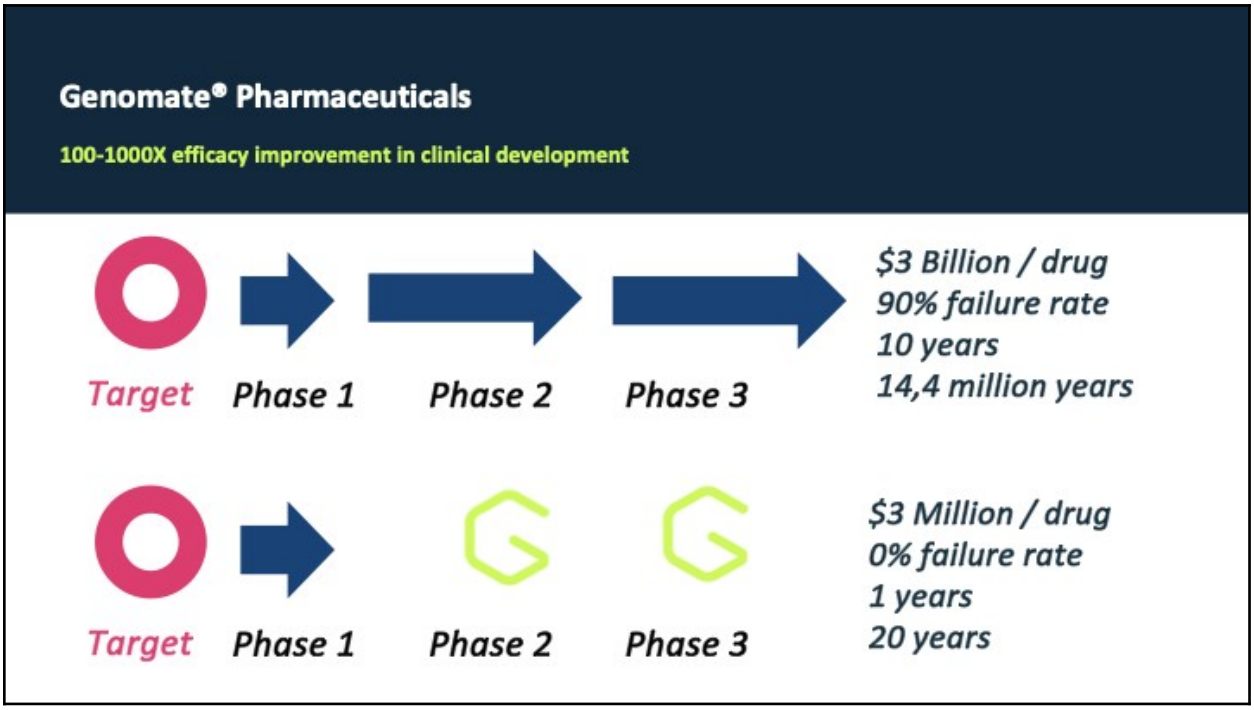


This is how it looks.

This is my last thought. I am most excited about how to shorten the 14 million years we theoretically would need to do all the clinical trials to match the right therapy for every cancer patient. In a review paper in 2019, the authors envisioned that by 2039 we will have clinical trials that do not compare drugs, but AI-based treatment assignment algorithms. This is how we can

shift the paradigm in medicine and test the personalized treatment selection methods, instead of individual therapies. We want to make sure that we don't have to wait until 2039. I think the time has come.

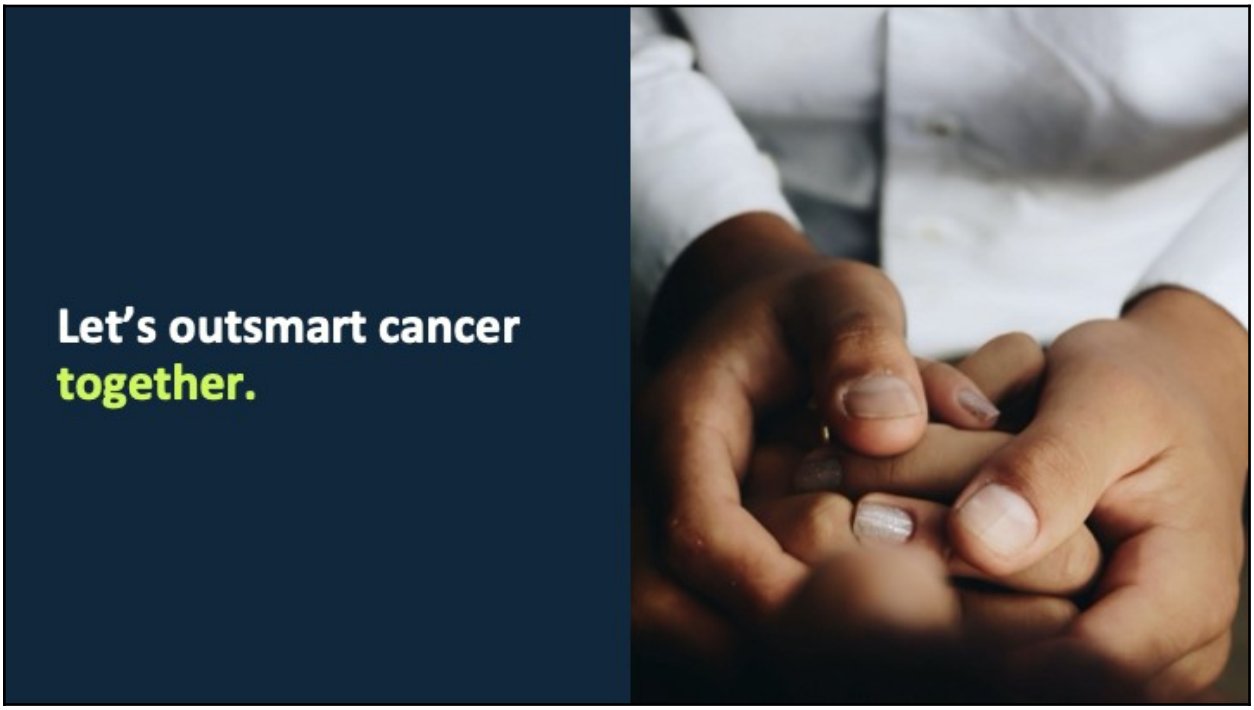
We can super accelerate clinical development of drugs in the future.



And because we can, if we have a validated platform to select patients to really benefit from a new targeted therapy, we hope that we can provide an accelerated superhighway for this drug to reach patients.

Luckily, I don't have to do it alone. I have a fantastic team of young researchers, molecular biologists, cancer biologists, scientists, and engineers, and I really thank them.

We are also part of a larger community. We are really happy and excited to be part of CancerX from the beginning.



We work together to outsmart cancer.

I'm excited to work with anybody who can contribute to this call.
Thank you for your invitation and your interest.

Roger Royse 32:16
The biomarkers that you're looking at, what are they? Is it DNA? RNA? Proteomics? Is it everything? Because it seems to me there's a million. Personally, I got several different reports, and they all said something different. I'm wondering what your inputs are?

Istvan Petak 32:46
Absolutely. So there's the problem that if you, for example, take a test, a molecular diagnostic test, that analyzes one possible biomarker, the report will report what's the best matching therapy based on that finding. But then, if you take different tests, which measure different things, like sequencing of the DNA, and you have maybe a point mutation here and a translocation there, and an alteration of another gene. Each can be linked to a specific possible therapy, and current test results release treatment options that match each genetic alteration. But those treatment options match those genetic alterations. There is no way to figure out which one to choose for this patient with this specific combination of that alterations. We have to combine all that we know about that patient, not just all the alterations and genetic events that are present in the same report, if it's a multi-gene test, but also we can combine all the reports the patient has; maybe a liquid biopsy test, and there's a solid tumor test, then we can use all this as an input to make an automated inference about which therapy to choose for this patient based on all the alterations, what we know about this patient.

Roger Royse 34:26
It looks to me like your market is oncologists and oncology practices. I've found that there tends to be a lot of physician resistance, especially to AI solutions. How is your market penetration? Are doctors actually using this?

Istvan Petak 34:53
We just graduated from Mayo Clinic's platform, Accelerate (a 30-week program that helps early-stage health tech AI startups get market ready). We were selected there. We were really happy to work with the doctors at Mayo. We used anonymized data to further validate our method, based on data present there. We are at the phase where we are looking for our first partners. The technology has been developed in the past 10 years. But really it's just one year ago when we started to develop this into a product and a solution. After we found the results of SHIVA01, we knew that we have something that we have to make available to patients and doctors.

I don't know yet what the level of traction and openness to adopt this will be. My first experience is that it's a good thing that this is an explainable system. It's very complex, but still built on human logic. It's not machine learning-based. We believe that we can use simple rule-based reasoning on a high scale to improve treatment decisions. Generally doctors like this idea that it's explainable and logical. You can explore the background of the reasoning on our portal. We can explain retrospectively why the system recommended one or the other therapy. That increases trust. In general, of course, we doctors have to understand that it's inevitable that we

will use algorithms to make better decisions, and because all data is now digitized, it makes it available for computers to run very complex algorithms.

In our case, purposefully, we are focusing on a niche problem, where we want to use the best algorithm to match the targeted therapy for the molecular profile. This is something where most doctors accept that a computational model can be better. Doctors are still needed, because, of course, it has to be combined with all the clinical information they know about the patient. They don't feel threatened by this. Maybe biologists think that they can do the same as we thave been doing for ten years, making individual literature searches for cancer patiens are more threatened, but they shouldn't be, because we have to work together to develop better solutions.

Richard Anders 38:08
That's a really exciting project that you're working on. I would love to spend more time looking at the articles and the slides, because there's a lot there to understand.

I can't help but wonder at the complexity of the question at a granular level. Some of the issues that you raise, for example, if you have three targets, and one is expressed 50%, and one is expressed 20%, and when you do a DNA profile, and the 50% one has a drug that matches it, but it's not a very high affinity drug, whereas the 20% one has a very high affinity drug, and you got four other things. Now there's toxicity that you have to add in, and certain drugs might induce higher mutations, and certain mutations might mutate more readily. There are just so many sets of issues that you have to deal with when you have reasonably sparse datasets, and I don't know 10,000 50,000 100,000. When you have combinations like this, you're probably talking about quintillions of datasets that you really need. As you start to deal with those things, you're putting in your own scientific understanding.

Do you constantly test this against what real results there are in a machine learning algorithm that undergirds what you're doing?

It would possibly be very helpful to check what you're doing and say, “Well, this rule may not be an appropriate rule,” or “You're wrong in this set of areas.” I'm just wondering how you think about that absurdly large set of incredibly complicated questions.

Istvan Petak 40:10
In the first decade of our developmental research we constantly updated our database and algorithm database and the algorithm, and during the research phase after every case. Once we were able to test the clinical performance of the model, we switched the method. Now we are only changing the evidence database and the algorithm if we have tested on validation data sets that the new model that includes a new rule, or a changed rule, performs better than the previous one. That's the really exciting thing that now because we have a fully automated reasoning system that makes a fully automated deduction or inference, we can test the performance of the whole system and therefore, on data sets. Therefore, we can test whether adding a new piece of evidence into our database, or changing any rule, improves or not our

ability to predict response to therapy. Because that's the challenge that we don't want a system that includes all possible evidence in the world, because PubMed is free via 30 million publications. It is not valuable if we gather all the information. That's something that large language models now do, but we want to make sure that what the model uses as a knowledge base is validated to be a high quality knowledge base and provides useful information to the model. We don't try to update the database to include all that is published and all that is known. But we gradually build it better and better. At the same time, we validate whether the model gets better or not. This is a very important aspect of this research.

Richard Anders 42:47
Is your validation retrospective or using segregated portions of the data set? In either case, are there significant issues with doing that kind of validation? Where do you validate prospectively more rigorously?

Are there subpockets of clinical indications and drugs where you find that you're especially effective? Even that has flaws when you're dealing with so many patients, but I'm just wondering if you have isolated some of those subpockets where it seems to be especially effective?

Roger Royse 43:29
That correlates to a question in the chat.
Do you have greater success in certain types of tumors? By mutation?

Istvan Petak 43:39
The answer to the first question is: yes. In the case of a software solution, you can run a trial on existing data, basically, prospectively, so it's a retrospective analysis, but without selecting a subset of data and without using the data to train the system. For example, in the SHIVA01 trial, we included all the patients, so there was no retrospective selection of which data to include or not, because that's the whole idea of a prospective trial on existing data, without the possible danger of selecting a false biomarker or the risks of a retrospective analysis. In the future, we will be able to use real world evidence databases and existing clinical trial datasets to validate software algorithms.
That's the answer to your first question.

We have a tendency to have more data on more frequent cancers, like lung cancer. It seems that the model is quite universal. The available evidence about mutations that have been frequently seen in certain tumors will affect the model. We constantly monitor the efficacy of the modality in different tumor types, and we publish all these results. Our plan is to list tumor types that we have enough data already to prove the performance. Those which were just too rare, or we didn't have access to datasets to analyze, and different treatment options.

This is the other question about the type of therapies. First of all, it's important to emphasize that we focus on molecularly-targeted agents with known monotherapy effects. That's our focus and in our output, we can also provide the list of drugs that have been validated based on the model. We will have a list of genes that are the optimal inputs, and we have a list of drugs that

have been validated that can be predicted to be effective or not, but the list will grow, for sure. We're sure we will see differences in performance, simply because of our understanding of the biology of different cancer genes.

Roger Royse 47:30
Stratis Telloglou asked about how to get some of these therapies, and referenced NK, CAR-T, dendritic vaccines, etc., that are very difficult to get in the US. Any advice? Or is that a part of what you can help advise on?

> From Stratis Telloglou in the chat: Nowadays there are a number of targeted treatments like NK cells, CAR-T cells, DK cells, vaccines, etc., being developed and regulated in some countries but not in others due to regulation constraints. Patients sometimes are the best advocates for themselves but it's quite tough to find out which country's medical systems/which hospitals offer this treatment while the internet is full of scam advertisements.. Any advice on how to resolve this issue?

Istvan Petak 47:46
One way it can already help oncologists is to provide more personalized care for cancer patients to support decisions between reimbursed treatment options. As shown in the neuroendocrine tumor case, I purposefully chose that one, to show that we can improve our treatment decisions between approved and reimbursed on-label therapies. I don't see this in practice many times. We should be able to use what we know about the molecular profile of the patient to make better decisions between treatments that are available.

Of course, most oncologists think about using comprehensive molecular information to choose off label therapy when they run out of approved treatment options. That's another issue. That's really a pain when oncologists and patients have to fight for reimbursement for a therapy that is off label. I hope that solutions like ours will accelerate and objectify whether that patient should receive that off label therapy based on the molecular profile. We want to help in this fight to get reimbursement for these molecularly-targeted therapies, based on individual molecular profiles. Ultimately, we hope we can convince payers to automatically approve therapies with a certain level of certainty or a threshold where we have a lot of evidence to show a very high correlation to outcomes.

Ultimately, we want approval for this as a companion diagnostic software platform that enables oncologists to use multiple different types of targeted therapies on label based on the molecular profile and get those reimbursed for patients. Otherwise, it will be an extremely painful thing to wait until all therapies are approved and reimbursed for all possible indications in all possible tumor types. We don't want to wait millions of years, of course. We want to do this now. I don't see any other way ahead than to have a validated, automated personalized treatment selection platform, like ours. Hopefully there will be others that we can compare to.

Mark Stoner 51:02

I'm the founder and CEO of BioCrowd, a biotech marketplace connecting clinical researchers with investors, patient groups, and communities using the blockchain. I lived in Paris for three years and had a call recently with the Institute Curie. We have been looking for a tie in with researchers and with that community. I'll send more information on that.

In another area, we've had three calls with NASA. We have a call next week.
I'll follow up on NASA and microgravity.

Istvan Petak 51:52
I have already been approached by NASA. I'm really happy to follow up with you on that opportunity as well. I'm really excited about working with them, based on their very special databank.

Roger Royse 52:25
There is a question in the chat: “You mentioned using patient tests without any time restriction as input, shouldn't this be restricted to a certain timeframe?”

> From the chat:
> Rick Davis, AnCan Foundation: You mentioned using patient tests without any time restriction as input. For an accurate result, shouldn't this be restricted to within a certain time frame? We know that somatic mutations disappear and germline mutations may revert to wildtype.

AM editorial on the notion of germline mutations reverting to wild type

Yes, germline mutations can revert to wild type, but it's unlikely to happen precisely:

True reversion

A true reversion is a back mutation that restores the original nucleotide change. However, it's highly unlikely that a single mutated base will mutate again and revert to the wild type. Anything is possible when dealing with mutations, so rare events can happen.

Istvan Petak 52:36
It's best if we have a test that was performed not long ago, and it's a constant debate whether we need a fresh diagnostic test or how old the test can be.

It's necessary to take a new test if the patient was treated with a molecularly-targeted agent, and there was an initial response and then a secondary resistance. This is when we know that there must be new driver alterations that were selected out to be responsible for the resistance. This is a situation when I would recommend a new biopsy, a tissue biopsy or liquid biopsy, and a new test.

On the other hand, I often experience that many doctors believe that we always need a new test. But the problem with that is that it delays the use of the information, and we often run out of

time between treatment lines. If the patient has not received targeted therapy with the initial response, I would use the existing molecular profiling data that we already have, maybe from the primary tumor, even though we know that cancer is heterogeneous, and there are new mutations that occur in the metastatic sites. Still, experience shows that we can choose a therapy based on the founding driver alterations that also are in most cases in the metastatic sites. I would not delay the actual treatment of patients to do tests with a new test all of the time.

Adrien Sipos 55:06
There is an equation here of timing of the therapy versus having more precision about what therapy should be given. What in your experience is the timing that we are talking about here? How long is the test taking versus the urgency about entering into a new treatment regimen?

Istvan Petak 55:41
Generally, we think that waiting for a test should not be longer than two weeks. That's the general opinion of oncologists as well. This is what we believe is biologically and clinically acceptable to wait. That's why I was worried about the time. This is a big challenge. We should be able to organize the molecular profiling of the patient before the first line therapy. This is very challenging. After the diagnosis of cancer, we should do all that we can to expedite molecular diagnostic testing to make it available for first line treatment decisions. At least we should do this always one line before. We always have to have a strategy and think ahead, what we will do next if the patient progresses and luckily now we have liquid biopsies that can be done faster, or it's easier to access the sample.

I hope that when an oncologist sees that in a higher percentage of patients we can provide meaningful information about the therapy for the patient, they will be more enthusiastic about ordering these tests and get these tests because today their frustration is that only a fraction of tests are useful for the clinical decision; therefore, they weigh this against the loss of time. That's why they choose not to wait for the results. But when they see that thankfully, for example for our technology, when we can make sense of the molecular information for a much higher percentage of patients, they may be more open to do whatever it needs to to get these tests done as soon as possible.

Roger Royse 58:05
I want to thank you, doctor, for being here.

Your contact information is in the chat below.

CHAT DISCUSSION

00:16:35 Brad Power: Semmelweis was a famous doctor in Vienna who deduced that doctors should wash their hands and be sterile to avoid transferring disease from sick patients. (He was actually Hungarian, and he worked also in Budapest. The medical university he worked at now is named after him, Semmelweis University.)
00:18:11 Richard Anders: Unfortunately, after saving a large number of women giving birth, his teachings were rejected for many years before others rediscovered and brought this basic idea forward again
00:18:24 Stratis Telloglou: Hello to everyone from Greece, A general question to Dr Petak Nowadays there are a number of targeted treatments like NK cells car t cells DK cells vaccines etc being developed and regulated in some countries but not in others due to regulation constraints. Patients sometimes are the best advocates for themselves but its quite tough to find out which country's medical systems/which hospitals offer this treatment while the internet is full of scam advertisements.. Any advice how to resolve this issue
00:18:37 ari akerstein: Reacted to "Semmelweis was a fam..." with 👍
00:20:22 ari akerstein: Reacted to "Unfortunately, after..." with 👍
00:21:38 ari akerstein: Replying to "Unfortunately, after..."

There’s a good book that discusses this at length. It’s called “Mastery”. One of the takeaways fwiw was that his approach was highly combative vs. collaborative. Politics is an unfortunate reality in getting adoption. It ended up becoming a political nightmare with a very sad outcome as many people died needlessly due to that rejection.
00:25:42 Richard Anders: Replying to "Unfortunately, after..."

True, but the story as I understand it was that the doctors in the hospital (this was a maternity ward) were arrogant and felt that he was disrespecting them by insisting they wash their hands. Whether a more politic person could have made this more palatable is an interesting question
00:25:45 ari akerstein: This is a great slide!
00:28:23 ari akerstein: Replying to "Unfortunately, after..."

Yes - agreed (people sometimes suck in human ways), that was my read as well. Takeaway was that it's not enough to be a brilliant scientist, it requires navigating the human landscape as well. Anyway, a good lesson for the brilliant among us is that a clean/awesome insight isn’t enough to reach impact.
00:42:56 Rick Davis, AnCan Foundation: Do your results to date show greater success in certain tumor types either by location or mutation?
00:46:34 Alina Luchian: We also have two questions in the chat:

From Stratis Telloglou - Nowadays they are a number of targeted treatments like NK cells car t cells DK cells vaccines etc being developed and regulated in some countries but not in others due to regulation constraints. Patients sometime are the best advocates for themselves but its quite tough to find out which country medical systems/which hospitals offer this treatment while the internet is full of scam advertisements.. Any advice on how to resolve this issue?

From Rick Davis - Do your results to date show greater success in certain tumor types either by location or mutation?
00:54:10 Alina Luchian: Here are some quick links of what Dr. Petak mentioned:
The performance analysis in the SHIVA01 trial (Nature):
https://www.nature.com/articles/s41698-021-00191-2

The ASCO 2024 abstracts:
https://meetings.asco.org/abstracts-presentations/237182
https://meetings.asco.org/abstracts-presentations/232329
00:57:50 Rick Davis, AnCan Foundation: You mentioned using patient tests without any time restriction as input. For an accurate result, shouldn't this be restricted to within a certain time frame? We know that somatic mutations disappear and germline mutations may revert to wildtype.
00:59:15 Saed Sayad: Thank you.
01:08:46 Rick Davis, AnCan Foundation: Most NGS tests are done within 2 weeks - not really an issue
01:10:43 Alina Luchian: Istvan.petak@genomate.health